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(54) Title: COMPOSITIONS AND METHODS FOR TREATING BONE DEFICIT CONDITIONS

(57) Abstract

Compounds containing two aromatic systems covalently linked through a linker containing one or more atoms, or "linker" defined as including a covalent bond per se so as to space the aromatic systems at a distance 1.5–15Å, are effective in treating conditions associated with bone deficits. The compounds can be administered to vertebrate subjects alone or in combination with additional agents that promote bone growth or that inhibit bone resorption. They can be screened for activity prior to administration by assessing their ability to effect the transcription of a reporter gene coupled to a promoter associated with a bone morphogenetic protein and/or their ability to stimulate calvarial growth in model animal systems.

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COMPOSITIONS AND METHODS FOR TREATING BONE DEFICIT CONDITIONS

Technical Field

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The invention relates to compositions and methods for use in limiting undesired bone loss in a vertebrate at risk of such bone loss, in treating conditions that are characterized by undesired bone loss or by the need for bone growth, in treating fractures, and in treating cartilage disorders. More specifically, the invention concerns the use of specific classes of compounds identified or characterized by a high throughput screening assay.

Background Art

Bone is not a static tissue. It is subject to constant breakdown and resynthesis in a complex process mediated by osteoblasts, which produce new bone, and osteoclasts, which destroy bone. The activities of these cells are regulated by a large number of cytokines and growth factors, many of which have now been identified and cloned. Mundy has described the current knowledge related to these factors (Mundy, G.R. Clin Orthop 324:24-28, 1996; Mundy, G.R. J Bone Miner Res 8:S505-10,

Although there is a great deal of information available on the factors which influence the breakdown and resorption of bone, information on growth factors which stimulate the formation of new bone is more limited. Investigators have searched for sources of such activities, and have found that bone tissue itself is a storehouse for factors which have the capacity for stimulating bone cells. Thus, extracts of bovine bone tissue obtained from slaughterhouses contain not only structural proteins which are responsible for maintaining the structural integrity of bone, but also biologically active bone growth factors which can stimulate bone cells to proliferate. Among these latter factors are transforming growth factor β , the heparin-binding growth factors (acidic and basic fibroblast growth factor), the insulin-like growth factors (insulin-like growth factor I and insulin-like growth factor II), and a recently described family of

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proteins called bone morphogenetic proteins (BMPs). All of these growth factors have effects on other types of cells, as well as on bone cells.

The BMPs are novel factors in the extended transforming growth factor ß superfamily. They were first identified by Wozney J. et al. Science (1988) 242:1528-34, using gene cloning techniques, following earlier descriptions characterizing the biological activity in extracts of demineralized bone (Urist M. Science (1965) 150:893-99). Recombinant BMP2 and BMP4 can induce new bone formation when they are injected locally into the subcutaneous tissues of rats (Wozney J. Molec Reprod Dev (1992) 32:160-67). These factors are expressed by normal osteoblasts as they differentiate, and have been shown to stimulate osteoblast differentiation and bone nodule formation in vitro as well as bone formation in vivo (Harris S. et al. J. Bone Miner Res (1994) 9:855-63). This latter property suggests potential usefulness as therapeutic agents in diseases which result in bone loss.

The cells which are responsible for forming bone are osteoblasts. As osteoblasts differentiate from precursors to mature bone-forming cells, they express and secrete a number of enzymes and structural proteins of the bone matrix, including Type-1 collagen, osteocalcin, osteopontin and alkaline phosphatase (Stein G. et al. Curr Opin Cell Biol (1990) 2:1018-27; Harris S. et al. (1994), supra). They also synthesize a number of growth regulatory peptides which are stored in the bone matrix, and are presumably responsible for normal bone formation. These growth regulatory peptides include the BMPs (Harris S. et al. (1994), supra). In studies of primary cultures of fetal rat calvarial osteoblasts, BMPs 1, 2, 3, 4, and 6 are expressed by cultured cells prior to the formation of mineralized bone nodules (Harris S. et al. (1994), supra). Like alkaline phosphatase, osteocalcin and osteopontin, the BMPs are expressed by cultured osteoblasts as they proliferate and differentiate.

Although the BMPs are potent stimulators of bone formation in vitro and in vivo, there are disadvantages to their use as therapeutic agents to enhance bone healing. Receptors for the bone morphogenetic proteins have been identified in many tissues, and the BMPs themselves are expressed in a large variety of tissues in specific temporal and spatial patterns. This suggests that BMPs may have effects on many

tissues other than bone, potentially limiting their usefulness as therapeutic agents when administered systemically. Moreover, since they are peptides, they would have to be administered by injection. These disadvantages impose severe limitations to the development of BMPs as therapeutic agents.

There is a plethora of conditions which are characterized by the need to enhance bone formation. Perhaps the most obvious is the case of bone fractures, where it would be desirable to stimulate bone growth and to hasten and complete bone repair. Agents that enhance bone formation would also be useful in facial reconstruction procedures. Other bone deficit conditions include bone segmental defects, periodontal disease, metastatic bone disease, osteolytic bone disease and conditions where connective tissue repair would be beneficial, such as healing or regeneration of cartilage defects or injury. Also of great significance is the chronic condition of osteoporosis, including age-related osteoporosis and osteoporosis associated with postmenopausal hormone status. Other conditions characterized by the need for bone growth include primary and secondary hyperparathyroidism, disuse osteoporosis, diabetes-related osteoporosis, and glucocorticoid-related osteoporosis. In addition, or alternatively, the compounds of the present invention may modulate metabolism, proliferation and/or differentiation of normal or aberrant cells or tissues.

There are currently no satisfactory pharmaceutical approaches to managing any of these conditions. Bone fractures are still treated exclusively using casts, braces, anchoring devices and other strictly mechanical means. Further bone deterioration associated with postmenopausal osteoporosis has been decreased or prevented with estrogens or bisphosphonates.

US Patent 5, 280, 040 discloses a class of compounds which are 3, 4-diaryl chromans. These compounds can be considered derivatives of 2,3,4 triphenyl butanol, where the hydroxy at the 1-position forms an ether with the ortho position of the phenyl group substituted at the 4-position of the butanol. The parent 3,4-diaryl chromans do not contain nitrogen atoms in the aromatic moieties or their linkers. A preferred compound, centchroman, contains a nitrogen substituent only in one of the

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substituents on a phenyl moiety. These compounds are disclosed in the '040 patent as useful in the treatment of osteoporosis.

In addition, the PCT application WO97/15308 published 1 May 1997 describes a number of classes of compounds that are active in the screening assay described below and are useful in treating bone disorders. These compounds, generically, are of the formulae

$$R^{a}_{m} \xrightarrow{Z}_{L-Ar^{2}}$$

$$Ar^{1}$$

wherein Ra is a non-interfering substituent;

m is an integer of 0-4;

each dotted line represents an optional π -bond;

each Z is independently N, NR, O, S, CR or CR₂, where each R is independently H or alkyl (1-6C);

X is O, S, SO or SO₂,

L is a flexible linker; and

Ar² is a substituted or unsubstituted 6-membered aromatic ring; or:

$$R^a_n$$
 $L-Ar^2$

wherein R* is a non-interfering substituent;

n is an integer of 0 and 5;

L is a flexible linker which does not contain nitrogen or is a constrained linker; and

Ar² is a substituted or unsubstituted phenyl or a substituted or unsubstituted naphthyl.

There remains a need for additional compositions which can ameliorate the effects of abnormalities in bone formation or resorption. The present invention

expands the repertoire of compounds useful for limiting or treating bone deficit conditions, and for other uses that should be apparent to those skilled in the art from the teachings herein.

5 <u>Disclosure of the Invention</u>

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The invention provides compounds that can be administered as ordinary pharmaceuticals and have the metabolic effect of enhancing bone growth or inhibiting resorption. The compounds of the invention can be identified using an assay for their ability to activate control elements associated with bone anabolic factors. Thus, the invention is directed to methods and compositions for treating bone disorders, which methods and compositions use, as active ingredients, compounds wherein two aromatic systems are coupled so as to be spaced apart from each other by about 1.5 to about 15 Angstroms. The thus-linked systems (including the linker coupling them) preferably include at least one nitrogen atom.

Therefore, the compounds useful in the invention can be described as having the formula Ar¹-linker-Ar², wherein each of Ar¹ and Ar² is independently an aromatic system and the linker portion of the formula spaces Ar¹ and Ar² apart by a distance of approximately 1.5-15 Angstroms. Ar¹, Ar² and the linker may optionally be substituted with non interfering substituents. In the useful compounds, there is preferably at least one nitrogen atom in either Ar¹, Ar² and/or the linker, independent of any substituents thereon. Preferably, the compounds of the invention contain at least one additional heteroatom selected from the group consisting of N, S and O, independent of any substituent.

Thus, in one aspect, the invention is directed to a method to treat a condition in a vertebrate animal characterized by a deficiency in, or need for, bone growth replacement and/or an undesirable level of bone resorption, which method comprises administering to a vertebrate subject in need of such treatment an effective amount of certain compounds of the formula:

$$Ar^{1}-I-Ar^{2}$$

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wherein each of Ar¹ and Ar² is independently substituted or unsubstituted phenyl, substituted or unsubstituted naphthyl, a substituted or unsubstituted aromatic system containing a 6-membered heterocycle, or a substituted or unsubstituted aromatic system containing a 5-membered heterocycle; and

L is a linker that provides spacing of 1.5-15Å.

In other aspects, the invention relates to pharmaceutical compositions for use in the method, and to the compounds for use in preparing a medicament for use in the method.

10 Brief Description of the Drawings

Figure 1 gives a schematic representation of the compounds used as active ingredients in the methods and compositions of the invention.

Figure 2 shows the dose response curve for a positive control compound, designated 59-0008.

Figures 3 and 4 show illustrative compounds of the invention and the results obtained with them in an *in vitro* test for stimulation of bone growth.

Figures 5A, 5B and 5C show structures and results of a screening assay for a group of compounds which varies the parameters of lead compound 59-0072.

Figures 6A, 6B and 6C show structures and results of a screening assay for a group of compounds which varies the parameters of lead compound 50-0197.

Figure 7 shows structures and results of a screening assay for a group of compounds which varies the parameters of lead compound 59-0145.

Figures 8A, 8B and 8C show structures and results of a screening assay for a group of compounds which varies the parameters of lead compound 59-0045.

Figure 9 shows the results in an ex vivo calvarial assay for various compunds of the invention.

Figure 10 shows the increase in bone volume effected by subcutaneous administration of compound 59-0145 in the OVX in vivo assay.

Figure 11 is a graphical representation of percent increase in trabecular bone in ovariectomized rats treated with compound 59-0145.

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Figure 12 presents graphs showing results of qCT and bone histomorphometri and serum osteocalcin levels in rats treated with compound 59-0145.

Figure 13 (41 pages) is a list of compounds used in screening for bone morphogenic activity according to the screening assay set forth herein.

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Modes of Carrying Out the Invention

A rapid throughput screening test for compounds capable of stimulating expression of a reporter gene linked to a BMP promoter (a surrogate for the production of bone morphogenetic factors that are endogenously produced) is described in WO96/38590 published 5 December 1996, the contents of which are incorporated herein by reference. This assay is also described as a portion of a study of immortalized murine osteoblasts (derived from a mouse expressing a transgene composed of a BMP2 promoter driving expression of T-antigen) in Ghosh-Choudhery, N. et al. Endocrinology (1996) 137:331-39. In this study, the immortalized cells were stably transfected with a plasmid containing a luciferase reporter gene driven by a mouse BMP2 promoter (-2736/114 bp), and responded in a dose-dependent manner to recombinant human BMP2.

Briefly, the assay utilizes cells transformed permanently or transiently with a constructs in which the promoter of a bone morphogenetic protein, specifically BMP2 or BMP4, is coupled to a reporter gene, typically luciferase. These transformed cells are then evaluated for the production of the reporter gene product; compounds that activate the BMP promoter will drive production of the reporter protein, which can be readily assayed. Over 40,000 compounds have been subjected to this rapid screening technique, and only a very small percentage are able to elicit a level of production of luciferase 5-fold greater than that produced by vehicle. Compounds that activate the BMP promoter share certain structural characteristics not present in inactive compounds. The active compounds ("BMP promoter-active compounds" or "active compounds") are useful in promoting bone or cartilage growth, and thus in the treatment of vertebrates in need of bone or cartilage growth.

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BMP promoter-active compounds can be examined in a variety of other assays that test specificity and toxicity. For instance, nonBMP promoters or response elements can be linked to a reporter gene and inserted into an appropriate host cell. Cytotoxicity can be determined by visual or microscopic examination of BMP promoter- and/or nonBMP promoter-reporter gene-containing cells, for instance. Alternatively, nucleic acid and/or protein synthesis by the cells can be monitored. For in vivo assays, tissues may be removed and examined visually or microscopically, and optionally examined in conjunction with dyes or stains that facilitate histologic examination. In assessing in vivo assay results, it may also be useful to examine biodistribution of the test compound, using conventional medicinal chemistry/animal model techniques.

As used herein, "limit" or "limiting" and "treat" or "treatment" are interchangeable terms. The terms include a postponement of development of bone deficit symptoms and/or a reduction in the severity of such symptoms that will or are expected to develop. The terms further include ameliorating existing bone or cartilage deficit symptoms, preventing additional symptoms, ameliorating or preventing the underlying metabolic causes of symptoms, preventing or reversing bone resorption and/or encouraging bone growth. Thus, the terms denote that a beneficial result has been conferred on a vertebrate subject with a cartilage, bone or skeletal deficit, or with the potential to develop such deficit.

By "bone deficit" is meant an imbalance in the ratio of bone formation to bone resorption, such that, if unmodified, the subject will exhibit less bone than desirable, or the subject's bones will be less intact and coherent than desired. Bone deficit may also result from fracture, from surgical intervention or from dental or periodontal disease.

By "cartilage defect" is meant damaged cartilage, less cartilage than desired, or cartilage that is less intact and coherent than desired.

Representative uses of the compounds of the present invention include: repair of bone defects and deficiencies, such as those occurring in closed, open and nonunion fractures; prophylactic use in closed and open fracture reduction; promotion of bone healing in plastic surgery; stimulation of bone ingrowth into noncemented prosthetic

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joints and dental implants; elevation of peak bone mass in premenopausal women; treatment of growth deficiencies; treatment of peridontal disease and defects, and other tooth repair processes; increase in bone formation during distraction osteogenesis; and treatment of other skeletal disorders, such as age-related osteoporosis, postmenopausal osteoporosis, glucocorticoid-induced osteoporosis or disuse osteoporosis and arthritis. The compounds of the present invention can also be useful in repair of congenital, trauma-induced or surgical resection of bone (for instance, for cancer treatment), and in cosmetic surgery. Further, the compounds of the present invention can be used for limiting or treating cartilage defects or disorders, and may be useful in wound healing or tissue repair.

Bone or cartilage deficit or defect can be treated in vertebrate subjects by administering compounds of the invention which have been identified through suitable screening assays and which exhibit certain structural characteristics. The compositions of the invention may be administered systemically or locally. For systemic use, the compounds herein are formulated for parenteral (e.g., intravenous, subcutaneous, intramuscular, intraperitoneal, intranasal or transdermal) or enteral (e.g., oral or rectal) delivery according to conventional methods. Intravenous administration will be by a series of injections or by continuous infusion over an extended period. Administration by injection or other routes of discretely spaced administration will generally be performed at intervals ranging from weekly to once to three times daily. Alternatively, the compounds disclosed herein may be administered in a cyclical manner (administration of disclosed compound; followed by no administration; followed by administration of disclosed compound, and the like). Treatment will continue until the desired outcome is achieved. In general, pharmaceutical formulations will include a compound of the present invention in combination with a pharmaceutically acceptable vehicle, such as saline, buffered saline, 5% dextrose in water, borate-buffered saline containing trace metals or the like. Formulations may further include one or more excipients, preservatives, solubilizers, buffering agents, albumin to prevent protein loss on vial surfaces, lubricants, fillers, stabilizers, etc. Methods of formulation are well known in the art and are disclosed, for example, in Remington's Pharmaceutical

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Sciences, Gennaro, ed., Mack Publishing Co., Easton PA, 1990, which is incorporated herein by reference. Pharmaceutical compositions for use within the present invention can be in the form of sterile, nonpyrogenic liquid solutions or suspensions, coated capsules, suppositories, lyophilized powders, transdermal patches or other forms known in the art. Local administration may be by injection at the site of injury or defect, or by insertion or attachment of a solid carrier at the site, or by direct, topical application of a viscous liquid. For local administration, the delivery vehicle preferably provides a matrix for the growing bone or cartilage, and more preferably is a vehicle that can be absorbed by the subject without adverse effects.

Delivery of compounds herein to wound sites may be enhanced by the use of controlled-release compositions, such as those described in WIPO publication WO 93/20859, which is incorporated herein by reference in its entirety. Films of this type are particularly useful as coatings for prosthetic devices and surgical implants. The films may, for example, be wrapped around the outer surfaces of surgical screws, rods, pins, plates and the like. Implantable devices of this type are routinely used in orthopedic surgery. The films can also be used to coat bone filling materials, such as hydroxyapatite blocks, demineralized bone matrix plugs, collagen matrices and the like. In general, a film or device as described herein is applied to the bone at the fracture site. Application is generally by implantation into the bone or attachment to the surface using standard surgical procedures.

In addition to the copolymers and carriers noted above, the biodegradable films and matrices may include other active or inert components. Of particular interest are those agents that promote tissue growth or infiltration, such as growth factors. Exemplary growth factors for this purpose include epidermal growth factor (EGF), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), transforming growth factors (TGFs), parathyroid hormone (PTH), leukemia inhibitory factor (LIF), and insulin-like growth factors (IGFs). Agents that promote bone growth, such as bone morphogenetic proteins (U.S. Patent No. 4,761,471; PCT Publication WO 90/11366), osteogenin (Sampath et al. Proc. Natl. Acad. Sci. USA (1987) 84:7109-13) and NaF (Tencer et al. J. Biomed. Mat. Res. (1989) 23: 571-89) are also preferred.

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Biodegradable films or matrices include calcium sulfate, tricalcium phosphate, hydroxyapatite, polylactic acid, polyanhydrides, bone or dermal collagen, pure proteins, extracellular matrix components and combinations thereof. Such biodegradable materials may be used in combination with nonbiodegradable materials, to provide desired mechanical, cosmetic or tissue or matrix interface properties.

Alternative methods for delivery of compounds of the present invention include use of ALZET osmotic minipumps (Alza Corp., Palo Alto, CA); sustained release matrix materials such as those disclosed in Wang et al. (PCT Publication WO 90/11366); electrically charged dextran beads, as disclosed in Bao et al. (PCT Publication WO 92/03125); collagen-based delivery systems, for example, as disclosed in Ksander et al. Ann. Surg. (1990) 211(3):288-94; methylcellulose gel systems, as disclosed in Beck et al. J. Bone Min. Res. (1991) 6(11):1257-65; and alginate-based systems, as disclosed in Edelman et al. Biomaterials (1991) 12:619-26. Other methods well known in the art for sustained local delivery in bone include porous coated metal protheses that can be impregnated and solid plastic rods with therapeutic compositions incorporated within them.

The compounds of the present invention may also be used in conjunction with agents that inhibit bone resorption. Antiresorptive agents, such as estrogen, bisphosphonates and calcitonin, are preferred for this purpose. More specifically, the compounds disclosed herein may be administered for a period of time (for instance, months to years) sufficient to obtain correction of a bone deficit condition. Once the bone deficit condition has been corrected, the vertebrate can be administered an anti-resorptive compound to maintain the corrected bone condition. Alternatively, the compounds disclosed herein may be administered with an anti-resorptive compound in a cyclical manner (administration of disclosed compound, followed by anti-resorptive, followed by disclosed compound, and the like).

In additional formulations, conventional preparations such as those described below may be used.

Aqueous suspensions may contain the active ingredient in admixture with pharmacologically acceptable excipients, comprising suspending agents, such as methyl

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cellulose; and wetting agents, such as lecithin, lysolethicin or long-chain fatty alcohols. The said aqueous suspensions may also contain preservatives, coloring agents, flavoring agents and sweetening agents in accordance with industry standards.

Preparations for topical and local application comprise aerosol sprays, lotions, gels and ointments in pharmaceutically appropriate vehicles which may comprise lower aliphatic alcohols, polyglycols such as glycerol, polyethylene glycol, esters of fatty acids, oils and fats, and silicones. The preparations may further comprise antioxidants, such as ascorbic acid or tocopherol, and preservatives, such as p-hydroxybenzoic acid esters.

Parenteral preparations comprise particularly sterile or sterilized products. Injectable compositions may be provided containing the active compound and any of the well known injectable carriers. These may contain salts for regulating the osmotic pressure.

If desired, the osteogenic agents can be incorporated into liposomes by any of the reported methods of preparing liposomes for use in treating various pathogenic conditions. The present compositions may utilize the compounds noted above incorporated in liposomes in order to direct these compounds to macrophages, monocytes, other cells and tissues and organs which take up the liposomal composition. The liposome-incorporated compounds of the invention can be utilized by parenteral administration, to allow for the efficacious use of lower doses of the compounds. Ligands may also be incorporated to further focus the specificity of the liposomes.

Suitable conventional methods of liposome preparation include, but are not limited to, those disclosed by Bangham, A.D. et al. J Mol Biol (1965) 23:238-252, Olson, F. et al. Biochim Biophys Acta (1979) 557:9-23, Szoka, F. et al. Proc Natl Acad Sci USA (1978) 75:4194-4198, Mayhew, E. et al. ______ (1984) 775:169-175, Kim, S. et al. Biochim Biophys Acta (1983) 728:339:348, and Mayer, et al. Biochim Biophys Acta (1986) 858:161-168.

The liposomes may be made from the present compounds in combination with any of the conventional synthetic or natural phospholipid liposome materials including

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phospholipids from natural sources such as egg, plant or animal sources such as phosphatidylcholine, phosphatidylethanolamine, phosphatidylglycerol, sphingomyelin, phosphatidylserine, or phosphatidylinositol. Synthetic phospholipids that may also be used, include, but are not limited to: dimyristoylphosphatidylcholine,

5 dioleoylphosphatidylcholine, dipalmitoylphosphatidylcholine and distearoylphosphatidycholine, and the corresponding synthetic phosphatidylethanolamines and phosphatidylglycerols. Cholesterol or other sterols. cholesterol hemisuccinate, glycolipids, cerebrosides, fatty acids, gangliosides, sphingolipids, 1,2-bis(oleoyloxy)-3-(trimethyl ammonio) propane (DOTAP), N-[1-10 (2,3-dioleoyl) propyl-N,N,N-trimethylammonium chloride (DOTMA), and other cationic lipids may be incorporated into the liposomes, as is known to those skilled in the art. The relative amounts of phospholipid and additives used in the liposomes may be varied if desired. The preferred ranges are from about 60 to 90 mole percent of the phospholipid; cholesterol, cholesterol hemisuccinate, fatty acids or cationic lipids may 15 be used in amounts ranging from 0 to 50 mole percent. The amounts of the present compounds incorporated into the lipid layer of liposomes can be varied with the concentration of their lipids ranging from about 0.01 to about 50 mole percent.

Using conventional methods, approximately 20 to 30% of the compound present in solution can be entrapped in liposomes; thus, approximately 70 to 80% of the active compound is wasted. In contrast, where the compound is incorporated into liposomes, virtually all of the compound is incorporated into the liposome, and essentially none of the active compound is wasted.

The liposomes with the above formulations may be made still more specific for their intended targets with the incorporation of monoclonal antibodies or other ligands specific for a target. For example, monoclonal antibodies to the BMP receptor may be incorporated into the liposome by linkage to phosphatidylethanolamine (PE) incorporated into the liposome by the method of Leserman, L. et al. Nature (1980) 288:602-604.

Veterinary uses of the disclosed compounds are also contemplated. Such uses would include limitation or treatment of bone or cartilage deficits or defects in

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domestic animals, livestock and thoroughbred horses. The compounds described herein can also modify a target tissue or organ environment, so as to attract bone-forming cells to an environment in need of such cells.

The compounds of the present invention may also be used to stimulate growth of bone-forming cells or their precursors, or to induce differentiation of bone-forming cell precursors, either in vitro or ex vivo. As used herein, the term "precursor cell" refers to a cell that is committed to a differentiation pathway, but that generally does not express markers or function as a mature, fully differentiated cell. As used herein, the term "mesenchymal cells" or "mesenchymal stem cells" refers to pluripotent progenitor cells that are capable of dividing many times, and whose progeny will give rise to skeletal tissues, including cartilage, bone, tendon, ligament, marrow stroma and connective tissue (see A. Caplan J. Orthop. Res. (1991) 9:641-50). As used herein, the term "osteogenic cells" includes osteoblasts and osteoblast precursor cells. More particularly, the disclosed compounds are useful for stimulating a cell population containing marrow mesenchymal cells, thereby increasing the number of osteogenic cells in that cell population. In a preferred method, hematopoietic cells are removed from the cell population, either before or after stimulation with the disclosed compounds. Through practice of such methods, osteogenic cells may be expanded. The expanded osteogenic cells can be infused (or reinfused) into a vertebrate subject in need thereof. For instance, a subject's own mesenchymal stem cells can be exposed to compounds of the present invention ex vivo, and the resultant osteogenic cells could be infused or directed to a desired site within the subject, where further proliferation and/or differentiation of the osteogenic cells can occur without immunorejection. Alternatively, the cell population exposed to the disclosed compounds may be immortalized human fetal osteoblastic or osteogenic cells. If such cells are infused or implanted in a vertebrate subject, it may be advantageous to "immunoprotect" these nonself cells, or to immunosuppress (preferably locally) the recipient to enhance transplantation and bone or cartilage repair.

Within the present invention, an "effective amount" of a composition is that amount which produces a statistically significant effect. For example, an "effective

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amount" for therapeutic uses is the amount of the composition comprising an active compound herein required to provide a clinically significant increase in healing rates in fracture repair; reversal of bone loss in osteoporosis; reversal of cartilage defects or disorders; prevention or delay of onset of osteoporosis; stimulation and/or augmentation of bone formation in fracture nonunions and distraction osteogenesis; increase and/or acceleration of bone growth into prosthetic devices; and repair of dental defects. Such effective amounts will be determined using routine optimization techniques and are dependent on the particular condition to be treated, the condition of the patient, the route of administration, the formulation, and the judgment of the practitioner and other factors evident to those skilled in the art. The dosage required for the compounds of the invention (for example, in osteoporosis where an increase in bone formation is desired) is manifested as a statistically significant difference in bone mass between treatment and control groups. This difference in bone mass may be seen, for example, as a 5-20% or more increase in bone mass in the treatment group. Other measurements of clinically significant increases in healing may include, for example, tests for breaking strength and tension, breaking strength and torsion, 4-point bending, increased connectivity in bone biopsies and other biomechanical tests well known to those skilled in the art. General guidance for treatment regimens is obtained from experiments carried out in animal models of the disease of interest.

The dosage of the compounds of the invention will vary according to the extent and severity of the need for treatment, the activity of the administered compound, the general health of the subject, and other considerations well known to the skilled artisan. Generally, they can be administered to a typical human on a daily basis on an oral dose of about 0.1 mg/kg-1000 mg/kg, and more preferably from about 1 mg/kg to about 200 mg/kg. The parenteral dose will appropriately be 20-100% of the oral dose.

Screening Assays

The osteogenic activity of the compounds used in the methods of the invention can be verified using *in vitro* screening techniques, such as the assessment of

transcription of a reporter gene coupled to a bone morphogenetic protein-associated promoter, as described above, or in alternative assays such as the following:

Technique for Neonatal Mouse Calvarial Assay (In vitro)

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This assay is similar to that described by Gowen M. & Mundy G. *J Immunol* (1986) 136:2478-82. Briefly, four days after birth, the front and parietal bones of ICR Swiss white mouse pups are removed by microdissection and split along the sagittal suture. The bones are incubated in BGJb medium (Irvine Scientific, Santa Ana, CA) plus 0.02% (or lower concentration) β-methylcyclodextrin, wherein the medium also contains test or control substances, at 37°C in a humidified atmosphere of 5% CO₂ and 95% air for 96 hours.

Following this, the bones are removed from the incubation media and fixed in 10% buffered formalin for 24-48 hours, decalcified in 14% EDTA for 1 week, processed through graded alcohols; and embedded in paraffin wax. Three µm sections of the calvaria are prepared. Representative sections are selected for histomorphometric assessment of bone formation and bone resorption. Bone changes are measured on sections cut 200 µm apart. Osteoblasts and osteoclasts are identified by their distinctive morphology.

Other auxillary assays can be used as controls to determine nonBMP promoter-mediated effects of test compounds. For example, mitogenic activity can be measured using screening assays featuring a serum-response element (SRE) as a promoter and a luciferase reporter gene. More specifically, these screening assays can detect signalling through SRE-mediated pathways, such as the protein kinase C pathway. For instance, an osteoblast activator SRE-luciferase screen and an insulin mimetic SRE-luciferase screen are useful for this purpose. Similarly, test compound stimulation of cAMP response element (CRE)-mediated pathways can also be assayed. For instance, cells transfected with receptors for PTH and calcitonin (two bone-active agents) can be used in CRE-luciferase screens to detect elevated cAMP levels. Thus, the BMP promoter specificity of a test compound can be examined through use of these types of auxillary assays.

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In vivo Assay of Effects of Compounds on Murine Calvarial Bone Growth Male ICR Swiss white mice, aged 4-6 weeks and weighing 13-26 gm, are employed, using 4-5 mice per group. The calvarial bone growth assay is performed as described in PCT application WO 95/24211. Briefly, the test compound or appropriate control vehicle is injected into the subcutaneous tissue over the right calvaria of normal mice. Typically, the control vehicle is the vehicle in which the compound was solubilized, and is PBS containing 5% DMSO or is PBS containing Tween (2 µl/10 ml). The animals are sacrificed on day 14 and bone growth measured by histomorphometry. Bone samples for quantitation are cleaned from adjacent tissues and fixed in 10% buffered formalin for 24-48 hours, decalcified in 14% EDTA for 1-3 weeks, processed through graded alcohols; and embedded in paraffin wax. Three to five µm sections of the calvaria are prepared, and representative sections are selected. for histomorphometric assessment of the effects on bone formation and bone resorption. Sections are measured by using a camera lucida attachment to trace directly the microscopic image onto a digitizing plate. Bone changes are measured on sections cut 200 µm apart, over 4 adjacent 1x1 mm fields on both the injected and noninjected sides of the calvaria. New bone is identified by its characteristic woven structure, and osteoclasts and osteoblasts are identified by their distinctive morphology. Histomorphometry software (OsteoMeasure, Osteometrix, Inc., Atlanta) is used to process digitizer input to determine cell counts and measure areas or perimeters.

Additional In Vivo Assays

Lead compounds can be further tested in intact animals using an in vivo, dosing assay. Prototypical dosing may be accomplished by subcutaneous, intraperitoneal or oral administration, and may be performed by injection, sustained release or other delivery techniques. The time period for administration of test compound may vary (for instance, 28 days as well as 35 days may be appropriate). An exemplary, in vivo subcutaneous dosing assay may be conducted as follows:

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In a typical study, 70 three-month-old female Sprague-Dawley rats are weight-matched and divided into seven groups, with ten animals in each group. This includes a baseline control group of animals sacrificed at the initiation of the study; a control group administered vehicle only; a PBS-treated control group; and a positive control group administered a compound (nonprotein or protein) known to promote bone growth. Three dosage levels of the compound to be tested are administered to the remaining three groups.

Briefly, test compound, positive control compound, PBS, or vehicle alone is administered subcutaneously once per day for 35 days. All animals are injected with calcein nine days and two days before sacrifice (two injections of calcein administered each designated day). Weekly body weights are determined. At the end of the 35-day cycle, the animals are weighed and bled by orbital or cardiac puncture. Serum calcium, phosphate, osteocalcin, and CBCs are determined. Both leg bones (femur and tibia) and lumbar vertebrae are removed, cleaned of adhering soft tissue, and stored in 70% ethanol for evaluation, as performed by peripheral quantitative computed tomography (pqCT; Ferretti, J. *Bone* (1995) 17:353S-64S), dual energy X-ray absorptiometry (DEXA; Laval-Jeantet A. *et al. Calcif Tissue Intl* (1995) 56:14-18; J. Casez *et al. Bone and Mineral* (1994) 26:61-68) and/or histomorphometry. The effect of test compounds on bone remodeling can thus be evaluated.

Lead compounds also be tested in acute ovariectomized animals (prevention model) using an *in vivo* dosing assay. Such assays may also include an estrogentreated group as a control. An exemplary subcutaneous dosing assay is performed as follows:

In a typical study, 80 three-month-old female Sprague-Dawley rats are weight-matched and divided into eight groups, with ten animals in each group. This includes a baseline control group of animals sacrificed at the initiation of the study; three control groups (sham ovariectomized (sham OVX) + vehicle only; ovariectomized (OVX) + vehicle only; PBS-treated OVX); and a control OVX group that is administered a compound known to promote bone growth. Three dosage levels of the compound to be tested are administered to the remaining three groups of OVX animals.

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Since ovariectomy (OVX) induces hyperphagia, all OVX animals are pair-fed with sham OVX animals throughout the 35 day study. Briefly, test compound, positive control compound, PBS, or vehicle alone is administered subcutaneously once per day for 35 days. Alternatively, test compound can be formulated in implantable pellets that are implanted for 35 days, or may be administered orally, such as by gastric gavage. All animals, including sham OVX/vehicle and OVX/vehicle groups, are injected intraperitoneally with calcein nine days and two days before sacrifice (two injections of calcein administered each designated day, to ensure proper labeling of newly formed bone). Weekly body weights are determined. At the end of the 35-day cycle, the animals' blood and tissues are processed as described above.

Lead compounds may also be tested in chronic OVX animals (treatment model). An exemplary protocol for treatment of established bone loss in ovariectomized animals that can be used to assess efficacy of anabolic agents may be performed as follows. Briefly, 80 to 100 six month old female, Sprague-Dawley rats are subjected to sham surgery (sham OVX) or ovariectomy (OVX) at time 0, and 10 rats are sacrificed to serve as baseline controls. Body weights are recorded weekly during the experiment. After approximately 6 weeks of bone depletion (42 days), 10 sham OVX and 10 OVX rats are randomly selected for sacrifice as depletion period controls. Of the remaining animals, 10 sham OVX and 10 OVX rats are used as placebo-treated controls. The remaining OVX animals are treated with 3 to 5 doses of test drug for a period of 5 weeks (35 days). As a postitive control, a group of OVX rats can be treated with an agent such as PTH, a known anabolic agent in this model (Kimmel et al. Endocrinology (1993) 132:1577-84). To determine effects on bone formation, the following procedure can be followed. The femurs, tibiae and lumbar vertebrae 1 to 4 are excised and collected. The proximal left and right tibiae are used for pqCT measurements, cancellous bone mineral density (BMD) (gravimetric determination), and histology, while the midshaft of each tibiae is subjected to cortical BMD or histology. The femurs are prepared for pqCT scanning of the midshaft prior to biomechanical testing. With respect to lumbar vertebrae (LV), LV2 are processed

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for BMD (pqCT may also be performed); LV3 are prepared for undecalcified bone histology; and LV4 are processed for mechanical testing.

Nature of the Compounds Useful in the Invention

All of the compounds of the invention contain two aromatic systems, Ar¹ and Ar², spaced apart by a linker at a distance of 1.5-15Å, and may preferably contain at least one nitrogen atom. A summary of the structural features of the compounds included within the invention is shown in Figure 1.

As shown, Ar¹ and Ar² may include various preferred embodiments. These are selected from the group consisting of a substituted or unsubstituted aromatic ring system containing a 5-membered heterocycle; a substituted or unsubstituted aromatic ring system containing a six-membered heterocycle; a substituted or unsubstituted naphthalene moiety, and a substituted or unsubstituted benzene moiety. There are 16 possible combinations of these embodiments, if Ar¹ and Ar² are considered distinguishable. As will be clear, however, the designation of one aromatic system as Ar¹ and the other as Ar² is arbitrary; thus there are only ten possible combinations. However, for simplicity, Ar¹ and Ar² are designated separately with the realization that the choice is arbitrarily made. All linkers described herein if not palindromic, are considered to link Ar¹ to Ar² or *vice-versa* whether or not the complementary orientation is explicitly shown (as it is in some cases). Thus, if Ar¹ and Ar² are different and a linker is specified as -CONR-, it is understood that also included is the linker -NRCO- when the designations Ar¹ and Ar² are retained.

The noninterfering substituents on the aromatic system represented by Ar¹ and the noninterfering substituents on the aromatic system represented by Ar² are represented in the formulas herein by R² and R³, respectively. Generally, these substituents can be of wide variety. Among substituents that do not interfere with (and in some instances may be desirable for) the beneficial effect of the compounds of the invention on bone in treated subjects are included alkyl (1-6C, preferably lower alkyl 1-4C), including straight or branched-chain forms thereof, alkenyl (1-6C, preferably 1-4C), alkynyl (1-6C, preferably 1-4C), all of which can be straight or branched chains

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or are aryl (6-10C) or alkylaryl (6-15C) or aryl alkyl (6-15C) and may contain further substituents. R^a and R^b may also include halogens, (e.g. F, Cl, Br and I); siloxy, OR, SR, NR₂, OOCR, COOR, NCOR, NCOOR, and benzoyl, CF₃, OCF₃, SCF₃, N(CF₃)₂. NO, NO₂, CN, SO, SO₂R, SO₃R and the like, wherein R is alkyl (1-6C) or is H. Similarly, these substituents may contain R' as a substitute for R wherein R' is aryl (6-10C) or alkylaryl (6-15C) or aryl alkyl (6-15C). Where R^a or R^b substituents are in adjacent positions in the aromatic system, they may combine to form a ring. Further, rings may be included in substituents which contain sufficient carbon and heteroatoms to provide this possibility.

The choice of noninterfering substituents depends on the overall nature of the system. For example, in compounds of the invention wherein two pyridine rings are linked through a saturated flexible linker, a CF₃ substituent para to the linker in each of the pyridine rings is particularly preferred. In those systems wherein a quinoline is coupled through a flexible conjugated or nonconjugated linker to a phenyl substituent or to a naphthyl substituent, an amino group para to the linker in the phenyl or naphthyl moiety is preferred. Particularly preferred amino groups are dimethylamino and diethylamino. In systems wherein a benzothiazole is coupled to phenyl through a flexible linker, preferred substituents on the phenyl moiety include alkoxy or alkylthio—in combination with halo, in particular, chloro. Also preferred is the presence of a diethylamino group in the phenyl moiety para to the position that is coupled to the linker. In general, the presence of a substituent in the phenyl moiety para to the position of joinder to the linker is preferred.

Generally, preferred noninterfering substituents include hydrocarbyl groups of 1-6C, including saturated and unsaturated, linear or branched hydrocarbyl as well as hydrocarbyl groups containing ring systems; halo groups, alkoxy, hydroxy, amino, monoalkyl- and dialkylamino where the alkyl groups are 1-6C, CN, CF₃, OCF₃ and COOR, and the like.

Although the number of R^a and R^b may typically be 0-4 (m) or 0-5 (n) depending on the available positions in the aromatic system, preferred embodiments

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include those wherein the number of R^a is 0, 1 or 2 and of R^b is 0, 1, 2 or 3, particularly 1 or 2.

The linker group, L, may be a covalent bond or any group having a valence of at least two and covering a linear distance of from about 1.5 to about 15 Angstroms, including those that contain cyclic moieties, that meet this spatial requirement. Useful linkers are divided, by definition herein, into three general categories: (1) flexible nonconjugating linkers, (2) flexible conjugating linkers, and (3) constrained linkers. The preferred choice of linker will depend on the choices for Ar¹ and Ar².

As defined herein, flexible nonconjugating linkers are those that link only one position of Ar1 to one position of Ar2, and provide only a single covalent bond or a single chain between Ar¹ and Ar². The chain may contain branches, but may not contain π -bonds (except in the branches) or cyclic portions in the chain. The linker atoms in the chain itself rotate freely around single covalent bonds, and thus the linker has more than two degrees of freedom. Particularly useful flexible nonconjugating linkers, besides a covalent bond, are those of the formulas: -NR-, -CR2-, -S-, or -O-, wherein R is H or alkyl (1-6C), more preferably H or lower alkyl (1-4C) and more preferably H. Also contemplated are those of the formulas: -NRCO-, -CONR-, -CR₂S-, -SCR₂-, -OCR₂-, -CR₂O-, -NRNR-, -CR₂CR₂-, -NRSO₂-, -SO₂NR-, -CR₂CO-, -COCR₂-, and -NR-NR-CO-CR₂- and its complement -CR₂-CO-NR-NR-, or -NRCR2CR2NR- or the thiolated counterparts, and particularly -NHCR2CR2NH-, including the isosteres thereof, such as -NRNRCSNR- and -NRNRCONR-. Also contemplated are those of the formulas: -NH(CH₂)₂NH-, -O(CR₂)₂O-, and -S(CR₂)₂S-, including the isosteres thereof. The optimum choice among flexible nonconjugating linkers is dependent on the nature of Ar¹ and Ar².

Flexible conjugating linkers are those that link only one position of Ar^1 to one position of Ar^2 , but incorporate at least one double or triple bond or one or more cyclic systems in the chain itself and thus have only two degrees of freedom. A flexible conjugating linker may form a completely conjugated π -bond linking system between Ar^1 and Ar^2 , thus providing for co-planarity of Ar^1 and Ar^2 . Examples of useful flexible conjugating linkers include: -RC=CR-; -N=N-; -C=C-; -RC=N-; -N=CR-;

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-NR-N=CR-; -NR-NR-CO-CR=CR-, -N=NCOCR₂-, -N=NCSCR₂-, -N=NCOCR₂CR₂, -N=NCONR-, -N=NCSNR-, and the like, where R is H or alkyl (1-6C); preferably H or lower alkyl (1-4C); and more preferably H.

Constrained linkers are those that have more than one point of attachment to

either or both Ar¹ and Ar² and, thus, generally allow for only one degree of freedom.

Constrained linkers most frequently form fused 5- or 6-membered cyclic moieties with Ar¹ and/or Ar² where either Ar¹ or Ar² has at least one substituent appropriately positioned to form a second covalent bond with the linker, e.g., where Ar² is a phenyl group with a reactive, ortho-positioned substituent, or is derivatized to the linker directly at the ortho position. (Although the aromatic moieties should properly be referred to as phenylene or naphthylene in such cases, generally the term "phenyl" or "naphthyl" is used herein to include both monovalent and bivalent forms of these moieties.) Examples of particularly useful constrained linkers include

and the like, where X is O, N, S or CR, and Y is CR₂ or C=O.

In one class of preferred embodiments, Ar¹ is an aromatic system containing a 5-membered heterocycle, of the formula:

$$R^{a}_{m}$$
 (1a)

or

 R^{a}_{m} (2a)

wherein Z is S, O, NR or -CR₂ in formula (1a) or CR in formula (2a), where each R is independently H or alkyl (1-6C), the dotted line represents an optional π -bond, each R^a is independently a noninterfering substituent as defined above, and m is an integer of 0-4.

In general, Ar² is phenyl, naphthyl, or an aromatic system containing a 5- or 6-membered heterocyclic ring. All may be unsubstituted or substituted with noninterfering substituents, R^b.

When Ar² is an aromatic system containing a six-membered heterocycle, the formula of said system is preferably:

$$R^{b}_{m}$$
or
$$R^{b}_{m}$$
 $Z = Z$

 $\begin{array}{c|c}
R^b_{m} & z = z \\
z & z \\
z - z
\end{array}$ (iv)

wherein each Z is independently a heteroatom selected from the group

15 consisting of S, O and N; or is CR or CR₂, the dotted lines represent optional π-bonds,

each R^b is independently a noninterfering substituent, and m is an integer of 0-4, with

the proviso that at least one Z must be a heteroatom.

Ar2 in these compounds may also have the formula

where R^b is a noninterfering substituent as defined above and n is an integer from 0 to 5.

Similarly, when Ar² is naphthyl, it may contain 0-5 R^b substitutions. When Ar² is an aromatic system containing a 5-membered heterocycle, preferred forms are those as described for Ar¹.

Thus, in one set of preferred compounds, Ar¹ is

$$R^{a}_{m}$$
 (1a)

or

 R^{a}_{m} (2a)

wherein each R^a is a noninterfering substituent, m is an integer of 0-4, the dotted line represents an optional π bond, and Z is O, S, NR or CR₂ in formula (1) or is CR in formula (2) wherein each R is independently H or alkyl (1-6C).

In one group of these compounds, L is a flexible conjugating or nonconjugating linker. In this group, when Z is NR, Ar² is preferably a substituted or unsubstituted aromatic system containing a 5-membered heterocycle or is

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wherein R^b is a noninterfering substituent and n is an integer of 0-5; and/or L is -N=N-, -N=CR-, -RC=CR-, -NRNR-, -CR₂NR-, -CR₂CR₂-, -NRCO- or -CONR-where R is H or alkyl (1-6C); and/or the dotted line represents a π bond.

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In these embodiments as well as in alternative embodiments of Ar², it is preferred that each R^b is independently halo, OR, SR, NR₂, NO, NO₂, OCF₃ or CF₃ wherein R is H or alkyl (1-6C), or R^b comprises an aromatic system.

Preferred compounds in this group are 59-0100, 59-103, 59-104, 59-105 and 59-106 (See Figure 13).

In another group of these compounds with flexible linkers, Z is S, and Ar^2 is preferably a substituted or unsubstituted aromatic system containing a 6-membered heterocycle or is of the formula

wherein R^b is a noninterfering substituent and n is an integer of 0-5, and/or L is -N=N-, -N=CR-, -RC=CR-, -NRNR-, -CR₂NR-, -CR₂CR₂-, -NRCO- or -CONR-where R is H or alkyl (1-6C); and/or the dotted line represents a π bond.

In such compounds, regardless of the choice of Ar², preferred are those compounds wherein each R^b is independently halo, OR, SR, NR₂, NO, NO₂, OCF₃ or CF₃ wherein R is H or alkyl (1-6C) or R^b comprises an aromatic system.

Both when Z is S and when Z is NR, it is preferred that m is 0 and/or each R^b is independently OR, SR or halo, where n=2 and at least one R^b is independently OR or SR and/or L is -NHCO- or -CR=CR-.

Preferred compounds in this group include compounds 59-002, 59-0070, 59-0072, 59-0099, 59-0102, the benzothiazole counterpart of 59-0104, 59-0144, 59-0147, 59-0149, 59-0186, 59-0187, 59-0192, 59-0193, 59-0195, 59-0197, 59-0202, 59-0204, 59-0205, 59-0206, 59-0207, 59-0208, and 59-0210, especially the benzothiazole counterpart of 59-0104 or compounds 59-0147, 59-0205 or 59-0210. (See Figure 13)

Z can also be CR, CR_2 or O; here it is also preferred that Ar^2 is

wherein R^b is a noninterfering substituent and n is an integer of 0-5, and/or L is -N=N-, -N=CR-, -RC=CR-, -NRNR-, -CR₂NR-, -CR₂CR₂-, -NRCO- or -CONR-where R is H or alkyl (1-6C), and/or the dotted line represents a π bond.

In these compounds, too, it is preferred that each R^b is independently halo, OR, SR, NR₂, NO, NO₂, OCF₃ or CF₃ wherein R is H or alkyl (1-6C) or R^b comprises an aromatic system. A preferred compound is 896-5005. (See Figure 4)

The compounds wherein Ar¹ is 1a or 2a as above may also contain a constrained linker.

In these compounds, preferred Z is S or NR; and/or those wherein L is selected from the group consisting of

; and/or

Ar² is

$$R^b_m$$

wherein R^b is a noninterfering substituent and m is 0-4.

Preferably, each R^b is independently halo, OR, SR, NR₂, NO, NO₂, OCF₃ or CF₃ wherein R is H or alkyl (1-6C) or R^b comprises an aromatic system. A preferred compound is 59-0124. (See Figure 13)

In another group of preferred embodiments, Ar1 is of the formula

$$R^a$$
 (3a)

wherein each R^a is independently a noninterfering substituent or is H and Z is NR, S or O, wherein R is alkyl (1-6C) or H, especially where Z is S and/or wherein Ar^2 is

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wherein R^b is a noninterfering substituent and n is an integer of 0-5,; and/or L is -N=N-, -N=CR-, -RC=CR-, -NRNR-, -CR₂NR-, -CR₂CR₂-, -NRCO- or -CONR- where R is H or alkyl (1-6C), and/or the dotted line represents a π bond. Especially preferred are those compounds where each R^b is independently halo, OR, SR, NR₂, NO, NO₂, OCF₃ or CF₃ wherein R is H or alkyl (1-6C) or R^b comprises an aromatic system.

In another group of compounds, Ar1 is

$$R^a_m$$
 (4a)

wherein R^a is a noninterfering substituent, m is an integer of 0-4, each dotted line represents an optional π-bond, each Z is independently N, NR, CR or CR₂, where each R is independently H or alkyl (1-6C) with the proviso that at least one Z is N or NR.

Particularly preferred members of this group are those wherein Ar¹ is

$$R^a_m$$
 (5a)

especially those wherein Ar₂ is

$$R^{b}_{n}$$
 R^{b}_{m} R^{b}_{m} (vi) or N (via)

wherein each R^b is independently a noninterfering substituent, and n is 0-5 and m is 0-4, and/or L is -N=N-, -RC=CR-, -RC=N-, -NRCO-, -NRCR₂-, -NRCR₂CR₂-, -NRCR₂CCR₂-, -NRCR₂CR₂-, -NRCR₂CR₂NR-, -NRCR=CRNR- or -NRCOCR₂NR-.

In general, preferably each R^b is independently halo, OR, SR, NR₂, NO, NO₂, OCF₃ or CF₃ wherein R is H or alkyl (1-6C) or R^b comprises an aromatic system.

In an especially preferred group, m is 0, each R^b is NR₂ or OR and n is 1 or 2, and/or L is -CR=CR-, -N=N- or -NRCO-, especially the compounds of formulas 59-0030, 59-0078, 59-0091, 59-0093, 59-0150, 50-0197, 59-0198, 59-0199 or 59-0480. (See Figure 13)

Also preferred are those wherein Ar¹ has formula (4a) or (5a) and wherein Ar₂ is substituted or unsubstituted quinolyl or naphthyl of the formula

$$R^{b}_{m} \qquad R^{b} \qquad R^{b}_{m} \qquad R^{b}$$

$$Or \qquad N \qquad (viii)$$

$$R^{b}_{m} \qquad R^{b} \qquad R^{b}_{m} \qquad R^{b}$$

$$Or \qquad N \qquad (ix)$$

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wherein each R^b is a noninterfering substituent and m is 0-4.

Preferred among these are those wherein L is -N=N-, -RC=CR-, -RC=N-, -NRCO-, -NRCR₂-, -NRCR₂CR₂-, -NRCR₂CO-, -NRNR-, -CR₂CR₂-, -NRCR₂CR₂-, -NRCR₂CR₂NR-, -NRCR=CRNR- or -NRCOCR₂NR-, and/or wherein each R^b is independently halo, OR, SR, NR₂, NO, NO₂, OCF₃ or CF₃ wherein R is H or alkyl (1-6C) or R^b comprises an aromatic system and m is 0, 1 or 2.

The compounds 59-0089, 59-0090, 59-0092 or 59-0094 are particularly preferred.

Ar is also preferably

$$R^{a}_{m}$$
 R^{a}_{m} R^{a

wherein each R² is a noninterfering substituent and m is 0-4, in particular where L is -N=N-, -RC=CR-, -RC=N-, -NRCO-, -NRCR₂-, -NRCR₂CR₂-, -NRCR₂CO-, -NRNR-, -CR₂CR₂-, -NRCR₂CR₂NR-, -NRCR=CRNR- or -NRCOCR₂NR-, and/or Ar² is

wherein R^b is a noninterfering substituent and n is an integer of 0-5. Especially preferred are compounds wherein each R^b is independently halo, OR, SR, NR₂, NO, NO₂, OCF₃ or CF₃ wherein R is H or alkyl (1-6C) or R^b comprises an aromatic system, in particular compounds 59-203, 59-285 or 59-286. (See Figure 13)

When Ar¹ is of formula (4a), L can also be a constrained linker.

In still another preferred set, Ar is

$$\begin{array}{cccc}
R^{a}_{m} & z-z \\
z-z & (9a)
\end{array}$$

wherein each R^a is independently a noninterfering substituent, m is an integer of 0-4, each Z is independently N or CR, where R is H or alkyl (1-6C), with the proviso that at least one Z must be N and at least one Z must be CR.

In these compounds, L is preferably a flexible conjugating or nonconjugating linker, and/or wherein Ar² is

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$$R^{b}_{n}$$
 (v) or Z^{z-z}_{z-z} (vi)

wherein each R^b is independently a noninterfering substituent, and in (vi) each Z is independently N or CR, where R is H or alkyl (1-6C), with the proviso that at least one Z must be a N and at least one Z must be CR.

5 Preferred such compounds have the formula

$$R^{a}_{m}$$
 or R^{b}_{n}

Preferred L embodiments in this group include -N=N-, -RC=CR-, -RC=N-,
-NRCO-, -NRCR₂-, -NRCR₂CR₂-, -NRCR₂CO-, -NRNR-, -CR₂CR₂-,
-NRCR₂CR₂NR-, -NRCR=CRNR- or -NRCOCR₂NR-; preferred for R^a and R^b are
halo, OR, SR, NR₂, NO, NO₂, OCF₃ or CF₃ wherein R is H or alkyl (1-6C) or R^a or R^b
comprise aromatic systems and each m and n is independently 0, 1 or 2.

In particular, compounds are preferred where L is -NHCR₂CR₂NH- and R^a is CF₃ para to L, especially compounds 59-0145, 59-0450, 59-0459 or 59-0483. (See Figure 13)

Finally, in another preferred group, Ar¹ is

wherein each R^a is a noninterfering substituent, and n is an integer of 0 and 5, and wherein L is a flexible linker that contains at least one nitrogen. In the alternative or in addition, Ar^2 is of the formula

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and L is -N=N-, -RC=CR-, -RC=N-, -NRCO-, -NRCR₂-, -NRCR₂CR₂-,

- -NRCR₂CO-, -NRNRCR₂CR₂-, -NRNRCR=CR-, -NRNRCOCR₂-,
- -NRNRCOCR=CR-, -NRNRCSCR₂-, -NRNRCSCR=CR-, -NRNRCONR-,
- -NRNRCSNR-, -NRNR-, -CR2CR2-, -NRCR2CR2NR-, -NRCR=CRNR- or
- -NRCOCR₂NR-. It is preferred that each R^b is independently halo, OR, SR, NR₂, NO, NO₂, OCF₃ or CF₃ wherein R is H or alkyl (1-6C) or R^b comprises an aromatic system.

Especially preferred are those compounds wherein L is -CR=CRCONRNR-,
-CR=CRCSNRNR-, -CR₂CONRNR- -CR₂CSNRNR-, -NRNRCONR- or
-NRNRCSNR- and/or R^b is -NR₂ and n=1 wherein R^b is in the para position, especially wherein R^a is -COOR and m is 1; most especially compounds 59-0045, 59-0095,
59-0096, 59-0097 and 59-0098. (See Figure 13)

As set forth above, several families of preferred embodiments are defined by specifying Ar^1 and Ar^2 , and L. In one such family, wherein Ar^1 is an aromatic system containing a 5-membered heterocyclic ring, the compound 59-0072, wherein Ar^1 is unsubstituted benzothiazole, the linker $(Ar^1 \rightarrow Ar^2)$ is NHCO, and Ar^2 is 2-methoxy-4-methylthiophenyl was used as a lead compound and variations of the structure studied. Figure 5 shows representative compounds synthesized to analyze the effects of the nature of the linker, various alternatives of Ar^1 wherein Z is O, NR or S, and the effect of substitution on the phenyl moiety, as well as the heterocycle.

Figure 5 gives the structures of these compounds, along with their maximum activity as compared to 59-0008 at 10 μM (the maximum for 59-0008) in the *in vitro* bone growth stimulation assay as well as the concentration at which 50% of maximum stimulation of the BMP promoter was obtained (EC₅₀). See Example 1 for the details of this assay. The results of this study indicate that the amide linker in 59-0072 can readily be substituted by -CH=CH- and that the substitution on the phenyl ring had advantageous effects in the order: 2-Cl-4-OMe=2,4-di-OMe=2-OMe-4-SMe >>3,4-di-OMe=4-OMe. In general, compounds 59-0205, 59-0104, 59-0107, 59-0210 and 59-0124 have the best activity in the primary screen, but only 59-0124 is active in the *ex vivo* calvarial assay described in Example 3.

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Similar structure/activity relationship studies were conducted for compounds wherein Ar¹ is quinoline. In this study, compound 50-0197, wherein Ar¹ is unsubstituted quinoline, the linker is -CH=CH-, and Ar² is p-dimethylaminophenyl was used as a lead compound. The compounds synthesized in this study are shown in Figure 6, along with their maximum stimulation characteristics and EC₅₀ in the assay of Example 1. The results of these studies showed that quinoxaline analogs are the most active in the assay, followed by quinoline; the linker can most preferably be -CH=CH- or -N=N- as judged by activity in the assay, but -CH=CH- is preferred *in vivo* due to its lack of toxicity. Preferred substituents on the phenyl ring in Ar² include 2,4-di-OMe; 4-NMe₂-2-OMe, and 4-NMe₂. For the compounds in Figure 6, 59-0282 and 50-0197 were moderately active and 59-0203 was highly active in the *ex vivo* calvarial assay described hereinabove as a modification of Gowen, M. and Mundy, G. *J. Immunol* (1986) 136:2478-2482.

Another group of compounds wherein Ar¹ and Ar² are pyridyl heterocycles was also studied. In this case, compound 59-0145 was used as the lead compound; the linker, the nature of the substituents R^a and R^b were varied. In one instance, a quinolyl residue was substituted for a pyrimidine residue as Ar². Representative compounds used in this study are shown in Figure 7, along with the data from the screening assay.

Using 59-0145 as a lead, a CF₃ group in one of Ar¹ and Ar² appeared essential; however, one of R^a or R^b could also be NO₂ or CN. The most preferred linker is -NHCH₂CH₂NH-; substitution on the amino groups in L by an alkyl group appeared to reduce activity. Enhanced chain lengths also led to loss of activity.

Preferred compounds in this group, which perform better than 59-0008 in the screening assay, included 59-0450, 59-0459, 59-0480, and 59-0483.

Finally, a series in which Ar¹ is 3-carboxyphenyl was studied using 59-0045 as the lead compound. In 59-0045, L is -NHN=CH- and Ar² is p-dimethylaminophenyl. Figure 8 shows the compounds synthesized in this series. Under the circumstances of this assay, analogs wherein R^b was, instead of a nitrogen-containing moiety, F, Cl, or OMe were inactive. Preferred compounds in this series are 59-0096 and 59-0098.

30 59-0098 is very active in the ex vivo calvarial assay described above.

Synthesis of the Compounds Useful in the Invention

Many of the compounds useful in the invention are commercially available and can be synthesized by art-known methods. Those compounds useful in the invention which are new compounds, can similarly be obtained by methods generally known in the art, as described in the Examples below.

The following examples are intended to illustrate, but not to limit, the invention.

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Preparation A

Compound 59-0008 used as a standard in the assays, was synthesized according to the procedure of McDonald, W. S., et al. Chem Comm (1969) 392-393; Irving, H. N. N. H. et al. Anal Chim Acta (1970) 49:261-266. Briefly, 10.0 g of dithizone was taken up in 100 ml EtOH and 50 ml AcOH and heated at reflux for 18 h. After cooling, this was diluted first with 100 ml water and then with 50 ml 1N NaOH. This was then further neutralized by the addition of 6 N NaOH to bring the pH to 5.0. This deep purple mixture was then concentrated on a rotavapor to remove organics. Once the liquid had lost all of its purple color, this was filtered to collect the dark precipitate. Purification by flash chromatography (4.5 x 25.7 cm; EtAc/Hep. (1:4); Rf 0.22) followed by recrystalization from EtOH gave 2.15 g (25% yield) of dark purple crystals, mp=184-185 °C. ¹H NMR (CDCl₃) 7.90 (d of d, J₁=7.7, J₂=2.2, 2H), 7.64 (hump, 1H), 7.49 (m, 3H), 7.02 (m, 1H), 6.91 (m, 2H), 6.55 (d, J=8.1, 1H). MS (EI) 254 (47, M+), 105 (26), 77 [100], 51 (27). HRMS (EI, M+) 254.0626 (calcd 254.0626182). Anal. Calcd for C₁₃H₁₀N₄S: C, 61.40; H, 3.96; N, 22.03. Found: C, 61.40; H, 4.20; N, 22.06.

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Example 1

High Throughput Screening

Several tens of thousands of compounds were tested in the assay system set forth in WO 96/38590, published 5 December 1996, and incorporated herein by reference. The standard positive control was 59-0008 (also denoted "OS8"), which is of the formula:

In more detail, the 2T3-BMP-2-LUC cells, a stably transformed osteoblast cell line described in Ghosh-Choudhury *et al. Endocrinology* (1996) 137:331-39, referenced above, was employed. The cells were cultured using α-MEM, 10% FCS with 1% penicillin/streptomycin and 1% glutamine ("plating medium"), and were split 1:5 once per week. For the assay, the cells were resuspended in a plating medium containing 4% FCS, plated in microtiter plates at a concentration of 5 x 10³ cells (in 50 μl)/well, and incubated for 24 hours at 37°C in 5% CO₂. To initiate the assay, 50 μl of the test compound or the control in DMSO was added at 2X concentration to each well, so that the final volume was 100 μl. The final serum concentration was 2% FCS, and the final DMSO concentration was 1%. Compound 59-0008 (10 μM) was used as a positive control.

The treated cells were incubated for 24 hours at 37°C and 5% CO₂. The medium was then removed, and the cells were rinsed three times with PBS. After removal of excess PBS, 25 µl of 1X cell culture lysing reagent (Promega #E153A) was added to each well and incubated for at least ten minutes. Optionally, the plates/samples could be frozen at this point. To each well was added 50 µl of luciferase substrate (Promega #E152A, 10 ml Promega luciferase assay buffer per 7 mg Promega luciferase assay substrate). Luminescence was measured on an

automated 96-well luminometer, and was expressed as either picograms of luciferase activity per well or as picograms of luciferase activity per microgram of protein.

In this assay, compound 59-0008 (3-phenylazo-1H-4,1,2-benzothiadiazine) exhibited a pattern of reactivity, as shown in Figure 2. The activity for compound 59-0008 was maximal at a concentration of approximately 3-10 µM and, more particularly, at about 3 µM, and thus provided a response of approximately 175 light emission units. Accordingly, other tested compounds were evaluated at various concentrations, and these results were compared to the results obtained for 59-0008 at 10 µM (which value was normalized to 100). For instance, any tested compound in Figure 3 and Figure 4 that showed greater activity than 10 µM of 59-0008 would result in a value over 100.

As shown in Figure 3 (46 sheets) and Figure 4 (28 sheets), several compounds were found to be particularly effective.

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Example 2

In vivo Calvarial Bone Growth Data

Compound 59-0008 was assayed *in vivo* according to the procedure described previously (see "*In vivo* Assay of Effects of Compounds on Murine Calvarial Bone Growth", *supra*). As compared to a vehicle control, compound 59-0008 induced a 4-fold increase in width of new calvarial bone.

In another experiment, 5 week old Swiss white mice were injected 3 times a day for 5 days over the calvaria with compound 59-0203 using PBS, 5% DMSO and 0.1% BSA as carrier. The drug was tested at 6 different doses, from 0.1-50 mg/kg/day. Animals were sacrificed 3 weeks after the injections started and calvariae were fixed, decalcified, and processed for histology. Bone histomorphometry measuring total bone area (BA/TV) confirms that FGF, used in every experiment as a positive control, shows an increase in the total bone area with all doses tested, but this increase is only significantly different from control at 1 and 5 mg/kg/day. The invention compound 59-0203 shows consistent increases over the 0.1-50 mg/kg/day range at a somewhat lower level than that obtained with FGF.

Similar results are obtained when new bone width in microns is measured. There was no new bone present in the control group. 59-0203 caused new bone formation at all doses, with a significant increase at 25-50 mg/kg/day. New bone as percentage of the total bone area was about 45% for the FGF positive control and from about 15% to 30% over the range of 0.1-50 mg/kg/day for 59-0203. There was no new bone present in the negative control.

Example 3

Ex vivo Calvarial Bone Growth Assay

A number of compounds, in particular, those studied in connection with lead compounds classified as hydrazone/hydrazides (H) exemplified by 59-0045, benzothiazoles (T) exemplified by 59-0104, bis-pyridines (P) exemplified by 59-0145, and quinolines/quinoxalines (Q) exemplified by 59-0197, were tested in the *ex vivo* calvarial assay described hereinabove. The results of this assay are shown in Figure 9. In this assay, histomorphotometry and osteoblast numbers are measured and effects are measured on an arbitrary scale from 1-3: i.e., 1, 1+, 2-, 2, 2+, 3-, 3, wherein 1 denotes "inactive." In this assay, for example, FGF scores 2-3.

The scores are assigned to bone formation on the ectocranial periosteal surface:

The area immediately surrounding midline suture is excluded from analysis.

Score

0 Toxicity. Cell necrosis, pyknotic nuclei, matrix disintegration.

A score of "1" is the bone forming activity seen in control cultures containing BGJb media + 0.1% bovine serum albumin. The periosteal surface is covered by one layer of osteoblasts (at about 50% of the bone surface, with the remaining 50% being covered by bone lining cells). A score of "1-" is assigned if less than 50% of the periosteal surface is covered by osteoblasts due to inhibitory activity or minor toxicity of the agents being tested. A score of "1+" is given if over 50% of the surface is covered by osteoblasts.

2 A moderate increase in bone forming activity. 20-40% of the periosteal surface is covered by up to two layers of osteoblasts. A score of "2-" is given if less than 20% of the surface is covered by

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two layers and "2+" if more than 40% of the surface is covered by two layers of osteoblasts.

3 A score of "3" is the bone forming activity seen in control cultures containing BGJb media + 0.1% BSA +10% fetal bovine serum. More than 20% of the periosteal surface is covered by three layers of osteoblasts. The cells appear plump (size can exceed 100μm2). A score of "3-" is given if less than 20% of the periosteal surface is covered by three layers of osteoblasts and or osteoblast size is less than 100μm2. A score of "3+" has never been observed.

In all samples, toxicity, ectopic new or woven bone formation associated with osteoblasts, and osteoblast size as reflections of relative activity are noted.

The results shown in Figure 9 represent those obtained when the measurements were made by two different groups. It is clear that a number of compounds tested have activity in this assay. From the results shown in Figure 9, 59-0073, 59-0030, 59-0070, 59-007, 59-0019, 59-0099, 59-0072 and 59-0103 show at least some indication of activity. 59-150 and 59-0104 showed activity when measured by one group but not the other; similarly, 50-0197 had this pattern. It appears that 59-0098 and 59-0203 are quite active in this assay and 59-0145 shows a consistent moderate activity.

Example 4

Stimulation of Bone Growth in Ovariectomized Rats (OVX Assay)

The compound 59-0145 was tested at various concentrations in the OVX assay conducted as described above. The increase in bone volume was measured by two different groups; one group found 5 µg/kg/day of 59-0145 gave 21% increase over control whereas the second group found a 71% increase. At 50 µg/kg/day, the first group found a 31% increase, and the second a 54% increase.

In another experiment, the lumbar vertebrae were measured and the above dosages of 59-0145 were shown to provide a beneficial effect, as shown in Figure 10.

In another experiment, 3 month old Sprague Dawley rats were ovariectomized and depleted for six weeks. At the end of the six weeks, treatment was started with subcutaneous administration of compound 59-0145. The treatment continued for 10

weeks. At the end of the 10 weeks animals were sacrificed, bones were collected for qCT measurements and histology; serum was also collected for osteocalcin determinations.

Figure 11 shows the percentage increase in trabecular bone (proximal tibia) compared to the placebo-treated group in chronic ovariectomized rats after 10 weeks of treatment. Compound 59-0145 causes significant increase in trabecular bone at doses of 50-500 µg/kg/day.

Figure 12 shows results of qCT and bone histomorphometry in proximal tibia in the first two panels, as well as serum osteocalcin levels at the time of sacrifice as a percentage increase compared to control group (OVX placebo-treated group).

Example 5

Chondrogenic Activity

Compounds 59-008, 59-0102 and 50-0197 were assayed for effects on the differentiation of cartilage cells, as compared to the action of recombinant human BMP-2. Briefly, a mouse clonal chondrogenic cell line, TMC-23, was isolated and cloned from costal cartilage of transgenic mice containing the BMP-2 gene control region driving SV-40 large T-antigen, generated as described in Ghosh-Choudhury *et al Endocrinology* 137:331-39, 1996. These cells were cultured in DMEM/10% FCS, and were shown to express T-antigen, and also to produce aggrecan (toluidine blue staining at pH 1.0) and Type-II collagen (immunostaining) by 7 days after confluence.

For measurement of alkaline phosphatase (ALP) activity, the technique of LF Bonewald *et al. J Biol Chem* (1992) 267:8943-49, was employed. Briefly, TMC-23 cells were plated in 96 well microtiter plates in DMEM containing 10% FCS at 4 x 10³ cells/well. Two days after plating, the cells were confluent and the medium was replaced with fresh medium containing 10% FCS and different concentrations of compounds or recombinant BMP-2. After an additional 2 or 5 days incubation, the plates were washed twice with PBS, and then lysing solution (0.05% Triton X-100) was added (100 µl/well). The cells were lysed by three freeze-thaw cycles of -70°C (30 min), followed by 37°C (30 min with shaking). Twenty microliters of cell lysates

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were assayed with 80 µl of 5 mM p-nitrophenol phosphate in 1.5 M 2-amino-2-methyl-propanol buffer, pH 10.3 (Sigma ALP kit, Sigma Chemical Co., St. Louis, MO) for 10 min at 37°C. The reaction was stopped by the addition of 100 µl of 0.5 M NaOH. The spectrophotometric absorbance at 405 nm was compared to that of p-nitrophenol standards to estimate ALP activity in the samples. The protein content of the cell lysates was determined by the Bio-Rad protein assay kit (Bio-Rad, Hercules, CA). Specific activity was calculated using these two parameters.

At day 2, compounds 59-0008 (10⁻⁹ M), 59-0102 (10⁻⁷ M) and 59-0197 (10⁻⁹ M) increased ALP levels approximately 3-, 2- and 2.5-fold, respectively, as compared to the vehicle control. Recombinant BMP2 at 100, 50 or 10 ng/ml induced ALP levels approximately 10-, 4- or 1.5-fold, respectively, as compared to the vehicle control.

Example 6

Synthesis of Exemplary Compounds

A. Compounds of the invention wherein Ar¹ is of formula (1a) or (2a) can be synthesized by the procedures described in Dryanska, V. and Ivanov, K. Synthesis (1976) 1:37-8, using the described embodiments of Ar² and the appropriate analogous heterocycle embodied in Ar¹ substituted for the benzothiazole shown. Alternates to the olefin linker described can also be prepared using standard methods.

Compounds of the invention represented by exemplary Compound 59-0234, wherein Z is O, L is -CH=CH-, and Ar² is 2,4-dimethyoxy-phenyl, including Compounds 59-0211 and 59-0233, were prepared according to the following procedure describing synthesis of Compound 59-0234. Briefly, to a N,N-dimethylformamide (DMF) solution of 2-methylbenzoxazole (1 mmol) and 2,4-dimethoxybenzaldehyde (1 mmol) was added lithium t-butoxide (2 mmol). The reaction mixture was heated at 130°C for 3h. After cooling to room temperature, the reaction mix was poured into ether and washed several times with water. The organic phase was dried over Na₂SO₄, filtered. and evaporated to dryness. The residue was dissolved in a minimal amount of hot ether and, on standing overnight, the crystalline product was collected by filtration.

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B. Exemplary Compound 59-0150 where Ar¹ is of formula 4a was synthesized according to the procedure of Zamboni et al. J Med Chem (1992) 35:3832-44. First, 2-triphenylphosphoniumquinaldine bromide was synthesized as follows. Quinaldine (200 mmols), NBS (200 mmols) and a catalytic amount of benzoyl peroxide (10 mmols) were dissolved in 1 L of anhydrous carbon tetrachloride, and the mixture was stirred under reflux for 72 h. The mixture was cooled to RT and washed with water. The organic layer was drawn off, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to a dark oil. The crude mixture was dissolved in 500 ml of acetonitrile, then triphenylphosphine (200 mmols) was added and the mixture was refluxed under nitrogen overnight. It was then cooled to RT and diluted with anhydrous ether. The precipitated solid was collected by filtration, washed thoroughly with anhydrous ether and dried in vacuo overnight, yielding 25 g of a tan crystalline solid which showed a single spot by TLC (silica gel, 5 % MeOH in DCM).

A Wittig reaction was then performed. Briefly, under anhydrous conditions, 0.738 g (1.68 mmol) 2-triphenylphosphoniumquinaldine bromide in dry THF was cooled to -78°C. 1.0 ml (2.5 mmol, 2.5 M in hexanes) n-butyl lithium was slowly added, and this was allowed to react for 20 min. 0.301 g (1.68 mmol) 4-(N,N-dimethylamino)-2-methoxybenzaldehyde was then added. After a few minutes, the cold bath was removed, and this was left at ambient temp. for 18 h. The reaction was quenched by the addition of aq. sat. NH4Cl. This was extracted with EtAc, and the organics washed with additional NH4Cl, sat. NaHCO3, and sat. NaCl. This was dried over anhydrous Na₂SO₄ and the solvent stripped on a rotavapor. After flash chromatography (3.8 x 18.0 cm; EtAc/Hep. (1:3); R_f 0.29), 0.135 g (26% yield) of a red solid was obtained, mp=185-187 °C. ¹H NMR (CDCl₃) 8.04 (t, J=9.0, 2H), 7.94 (d, J=16.5, 1H), 7.74 (d, J=8.1, 1H), 7.73 (d, J=8.5, 1H), 7.66 (t of d, J_t=7.6, J_d=1.4, 1H), 7.61 (d, J=8.8, 1H), 7.43 (t of d, J_t=7.6, J_d=1.1, 1H), 7.29 (d, J=16.6, 1H), 6.37 (d of d, J₁=8.7, J₂=2.4, 1H), 6.22 (d, J=2.4, 1H), 3.93 (s, 3H), 3.03 (s, 6H)... Anal. Calcd for C₂0H₂0N₂O: C, 78.92; H, 6.62; N, 9.20. Found:

- C. Exemplary Compound 59-0209 was synthesized according to the procedure of McOmie, J. F. W.; and West, D. E., Org Synth, Collect Vol V (1973) 412. Under anhydrous conditions, 0.510 g (1.95 mmol) NNC 59-0198 was slowly treated with 0.38 ml (3.9 mmol) BBr3 in dry CH2Cl2 at -78°C. After 15 min, this was 5 allowed to warm to RT. After 2 h, the reaction was re-cooled to -78°C, and was then quenched by the addition of 1.6 ml (12 mmol) TEA in 25 ml MeOH. After 10 min. this was again allowed to warm to ambient temperature. After 1 h, this was concentrated to dryness on a rotavapor, and twice slurred in MeOH and re-stripped. Purification by flash chromatography (3.0 x 25.6 cm; EtAc/Hep. (1:2); Rf 0.25) gave 10 0.20 g (41% yield) of a slightly yellow solid, mp=271-272 °C (dec.). H NMR (DMSO-d6) 9.77 (s, 1H), 8.31 (d, J=8.6, 1H), 7.96 (d, J=8.6, 1H), 7.92 (d, J=8.3, 1H), 7.82 (d, J=8.6, 1H), 7.74 (d, J=16.6, 1H), 7.72 (t, J=7.6, 1H), 7.58 (d, J=8.6, 2H), 7.53 (t, J=7.6, 1H), 7.26 (d, J=16.5, 1H), 6.83 (d, J=8.6, 2H). Anal. Calcd for C₁₇H₁₃NO: C, 82.57; H, 5.30; N, 5.66. Found:
- D. Exemplary Compound 59-0019 was synthesized as follows: to a xylene solution of 2-methylquinoxaline (10 mmol) and 4-dimethylaminobenzaldehyde (10 mmol) was added piperdine (2 ml). The solution was heated at reflux for 1 day, at which time DBU (200 μL) was added and reflux continued for another 2 days. The solution was cooled to RT and extracted with 1 M citric acid. The aqueous phase was repeatedly extracted with ether. The organic phases were pooled, dried over Na₂SO₄, filtered and evaporated to dryness. The residue was chromatographed on silica gel. The product was eluted using 8:1:1 dicholormethane:ether: hexane. Fractions containing pure product were pooled and evaporated to dryness. The residue was triturated with ether and filtered to give the desired compound.
- E. Exemplary Compound 59-0183 and related Compound 59-0182 were synthesized according to the following procedure. Briefly, quinaldic acid (0.5 mmol) and HATU (0.5 mmol) were dissolved in 2.5 mL of anhydrous DMF in a vial and the solution was stirred at room temperature (RT). Diisopropylethyamine (1 mmol) was added dropwise to the above stirred solution and the mixture was stirred for 15 min.

 The appropriate amine (0.5 mmol) was then added all at once to the above stirred

mixture, and the mixture was stirred overnight at RT. It was then diluted with 25 mL of cold water with vigorous stirring, the precipitate was collected by filtration and washed thoroughly with water several times, and then dried *in vacuo* overnight. The product was purified by flash column chromatography over silica gel eluting with dichloromethane. The pure product was obtained as a tan powder.

- F. Exemplary Compound 59-0209 was synthesized according to the following procedure. Under anhydrous conditions, 0.510 g (1.95 mmol) NNC 59-0198 was slowly treated with 0.38 ml (3.9 mmol) BBr3 in dry CH2Cl2 at -78°C. After 15 min, this was allowed to warm to RT. After 2 h, the reaction was re-cooled to -78°C, and was then quenched by the addition of 1.6 ml (12 mmol) TEA in 25 ml 10 MeOH. After 10 min, this was again allowed to warm to ambient temperature. After 1 h, this was concentrated to dryness on a rotavapor, and twice slurred in MeOH and re-stripped. Purification by flash chromatography (3.0 x 25.6 cm; EtAc/Hep. (1:2); Rf 0.25) gave 0.20 g (41% yield) of a slightly yellow solid, mp=271-272 °C (dec.). ¹H 15 NMR (DMSO-d6) 9.77 (s, 1H), 8.31 (d, J=8.6, 1H), 7.96 (d, J=8.6, 1H), 7.92 (d, J=8.3, 1H), 7.82 (d, J=8.6, 1H), 7.74 (d, J=16.6, 1H), 7.72 (t, J=7.6, 1H), 7.58 (d, J=8.6, 2H), 7.53 (t, J=7.6, 1H), 7.26 (d, J=16.5, 1H), 6.83 (d, J=8.6, 2H). Anal. Calcd for C₁₇H₁₃NO: C, 82.57; H, 5.30; N, 5.66. Found:
- G. Other embodiments wherein AR¹ is of formula (4a) can be synthesized 20 as follows:
 - a. Quinoline azo compounds (59-0030 and 59-0078) may be prepared by reaction of 2-aminoquinoline with a nitrosobenzene (Brown, E. V., et al, J Org Chem (1961) 26:2831-33; Brown, E. V; ______ (1969) 6:571-73).
- b. Azo derivatives may be obtained by reaction of 2-aminoquinolines with aldehydes, Morimoto, T., et al., Chem Pharm Bull (1977) 25:1607-09; Renault, J., et al., Hebd Seances Acad Sci, Ser C (1975) 280:1041-43; and Lugovkin, B. P.; Zh Obshch Khim (1972) 42:966-69.
- c. Imino derivatives may be obtained by reaction of 2formylquinolines with anilines, Tran Quoc Son, et al., (1983) 21:22-26; Hagen,

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V. et al. Pharmazie (1983) 38:437-39; and Gershuns, A. L., et al., Tr Kom Anal Khim, Akad Nauk SSSR (1969) 17:242-50.

- d. Alternatively conjugated linkers can be formed by bromination of the olefin of 50-0197 with Br₂ in AcOH followed by elimination with DBU as set forth in Zamboni *et al. J Med Chem* (1992) 35:3832-44
- H. Analogs having the constrained linker depicted below:

may be synthesized by reference to the methods described in Gorbulenko, N.V. et al. Dokl Akad Nauk Ukr SSR (1991) 5:117-23, substituting the 6-membered heterocycle for benzothiazole.

Related, compounds having the constrained linker depicted below:

15 may be synthesized by reference to the methods described in the following publications: Chaurasia, M.R. & Sharma, A.J. Acta Cienc Indica Chem (1992) 18:419-22; Kandeel, Maymona M., in Phosphorus, Sulfur, Silicon, Relat Elem (1990) 48:149-55; Salem, M.A. & Soliman, E.A. Egypt J Chem (1985) 27:779-87; Garin, J. et al. Synthesis (1984) 6:520-22, and Ayyangar N. R. et al. Dyes and Pigments (1990) 13:301-10.

I. Exemplary Compound 59-0145 can be synthesized according to the following method. Briefly, a mixture of 2-chloro-5-trifluoromethylpyridine (15 mmol), ethylenediamine (6 mmol), and diisopropylethylamine (18 mmol) was heated at reflux for 18 h. After cooling to room temperature, the solid mass was triturated with

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dichloromethane. The product was filtered and then suspended in hot EtOAc:CHCl₃ (50:50, 800 mL) and filtered to remove insoluble material. The volume was reduced to ~200 mL by heating on a steam bath. On standing, crystals of pure product were deposited.

Related compounds may be synthesized by reference to the method described for Compound 59-0145, and by reference to the methods described in the following publications: Tzikas, A.& Carisch, C., US Patent No. 5,393,306, issued February 28, 1995; Herzig, P.& Andreoli, A., EP 580554, published January 26, 1994; Pohlke, R. & Fischer, W., DE 3938561, published May 23, 1991. Analogs containing the structure O-(CH₂)_n-O may be synthesized by reference to the previous citations, as well as the following publications: Kawato, T. & Newkome, G. *Heterocycles* (1990) 31:1097-104; Kameko, C. & Momose, Y. *Synthesis* (1982) 6:465-66; Tomlin, C.D.S. *et al.*, GB 1161492, published August 13, 1969.

- J. Exemplary Compound 59-0097 and exemplary Compound 59-0201 were synthesized according to the following general procedure. Briefly, the isothiocyanate or isocyanate (1 mmol) was dissolved in 5 mL of anhydrous DMF in a vial and the solution was stirred at room temperature (RT). Diisopropylethyamine (2 mmol) was added dropwise to the above stirred solution followed by 3-hydrazinobenzoic acid (1 mmol), and the mixture was stirred overnight at RT. It was then diluted with 50 mL of cold water with vigorous stirring. The precipitate was collected by filtration, washed thoroughly with water several times, and then dried in vacuo overnight. The product was purified by flash column chromatography over silica gel eluting with 5 % methanol in dichloromethane. The pure product was obtained as a red to purple powder. The compounds of the invention are produced by substituting for at least one phenyl group the appropriate heterocycle.
- K. Compounds of the class represented by exemplary Compound 59-0045 can be synthesized using standard procedures for the synthesis of phenyl hydrazones of aromatic aldehydes, as described in any organic textbook. The synthesis of exemplary Compound 59-0045 may be performed as follows. Briefly, a suspension of 3-hydrazinobenzoic acid (1 mmol), p-dimethylaminobenzaldehyde (1 mmol), and AcOH

(50 μL) in EtOH:H₂O (4 mL:1 mL) was heated at 105°C in a sealed vial for 3 h. After cooling, a bright yellow solid was removed by filtration. The solid was washed with cold MeOH and then with ether to give pure product.

- L. Exemplary Compound 59-0096 and related, exemplary Compounds 59-0098, 59-0095, 59-0107, 59-0108, 59-0109, 59-0110 and 59-0200 may be synthesized according to the following general procedure. Briefly, the appropriate carboxylic acid (1 mmol) and HATU ([O-(7-azabenzotriazol-1-yl)-1,1,3,3-tritetramethyluronium hexafluorophosphate]; 1 mmol) were dissolved in 5 mL of anhydrous DMF in a vial and the solution was stirred at room temperature (RT). Diisopropylethyamine (3 mmol) was added dropwise to the above stirred solution and the mixture was stirred for 15 min. 3-Hydrazinobenzoic acid (1 mmol) was then added all at once to the above stirred mixture and the mixture was stirred overnight at RT. It was then diluted with 50 mL of cold water with vigorous stirring and the precipitate was collected by filtration and washed thoroughly with water several times and then dried in vacuo overnight. The product was purified by flash column chromatography over silica gel eluting with 5 10 % methanol in dichloromethane. The pure product was obtained as a tan crystalline solid.
- M. Exemplary Compound 59-0097 and exemplary Compound 59-0201 were synthesized according to the following general procedure. Briefly, the isothiocyanate or isocyanate (1 mmol) was dissolved in 5 mL of anhydrous DMF in a vial and the solution was stirred at room temperature (RT). Diisopropylethyamine (2 mmol) was added dropwise to the above stirred solution followed by 3-hydrazinobenzoic acid (1 mmol), and the mixture was stirred overnight at RT. It was then diluted with 50 mL of cold water with vigorous stirring. The precipitate was collected by filtration, washed thoroughly with water several times, and then dried in vacuo overnight. The product was purified by flash column chromatography over silica gel eluting with 5 % methanol in dichloromethane. The pure product was obtained as a red to purple powder.
- N. Exemplary Compound 59-0125 where R¹ is methoxy, m is 1, the linker is azo and Ar² is di(2-hydroxyethyl) amino, and related compounds having an azo

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linker can be prepared in a manner similar to that described by Alberti, G. et al. Chim Ind (Milan) (1974) 56:495-97.

O. Exemplary Compound 59-0124 and related, constrained analogs having the structure depicted below:

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may be synthesized by reference to the methods described in Gorbulenko, N.V. et al. Dokl Akad Nauk Ukr SSR (1991) 5:117-23.

Related, constrained analogs having the structure depicted below:

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may be synthesized by reference to the methods described in the following publications: Chaurasia, M.R. & Sharma, A.J. Acta Cienc Indica Chem (1992) 18:419-22; Kandeel, Maymona M., in Phosphorus, Sulfur, Silicon, Relat Elem (1990) 48:149-55; Salem, M.A. & Soliman, E.A. Egypt J Chem (1985) 27:779-87; Garin, J. et al. Synthesis (1984) 6:520-22, or according to the representative procedure described in Ayyangar N. R. et al. Dyes and Pigments (1990) 13:301-10.

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Claims

1. A method to treat a condition in a vertebrate animal characterized by a deficiency in, or need for, bone growth or replacement and/or an undesirable level of bone resorption, which method comprises administering to a vertebrate subject in need of such treatment an effective amount of a compound of the formula:

wherein each of Ar¹ and Ar² is independently a substituted or unsubstituted phenyl, substituted or unsubstituted naphthyl, substituted or unsubstituted aromatic system containing a 6-membered heterocycle or a substituted or unsubstituted aromatic system containing a 5-membered heterocycle; and

L is a linker which spaces Ar¹ from Ar² at a distance of 1.5Å-15Å.

2. The method of claim 1 with the proviso that in the compound of formula (1), if Ar^{1} is

and L is .

Ar² cannot be

wherein

5 R¹ is selected from the group consisting of:

H, OH, C1-C4 alkyl, C1-C4 alkoxy, C1-C4 alkylthio, halo and (C1-C12)alkyl-carbonyloxy;

R² is selected from the group consisting of:

H, OH, halo, C1-C6 alkyl, C1-C6 alkenyl, C1-C6 alkoxy and (C1-C12)alkylcarbonyloxy;

R³ is selected from the group consisting of:

H, OH, halo, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 alkenyl and (C1-C12)alkyl-carbonyloxy;

R⁴ is selected from the group consisting of:

15 H, OH, halo, C1-C6 alkyl, C1-C6 alkoxy and (C1-C12)alkyl-carbonyloxy;

R⁵ is selected from the group consisting of:

H, halo, C1-C6 alkyl, C1-C6 alkoxy, -OC(=O)Me, phthalimide and (C1-C12)alkyl-carbonyloxy;

R⁶ is selected from the group consisting of:

20 H, OH, -NH₂, Cl-C4 alkyl and C1-C4 alkoxy;

R⁷ is selected from the group consisting of:

H, C1-C4 alkyl, (C1-C4)alkyl-carbonyl and (C7-C10)arylalkyl;

R⁸ is selected from the group consisting of:

H, OH, halo, -CF₃, C1-C4 haloalkyl, C1-C4 alkyl, C1-C4 alkoxy,

5 -NHC(=0)Me and -N(C1-C4 alkyl)₂;

R⁹ is selected from the group consisting of:

H, OH, halo, -CN, -NO₂, C1-C4 haloalkyl, C1-C8 alkyl, C1-C8 alkoxy, -NHC(=O)Me and -OC(=O)Me;

R¹⁰ is selected from the group consisting of:

H, OH, halo, -CN, -NO₂, C1-C4 haloalkyl, -CO₂H, C1-C12 alkyl, C1-C12 alkoxy, phenyl, C1-C12 alkenyl, (C1-C4)alkoxycarbonyl, -NHC(=O)Me, (C1-C4)alkylcarbonyl, (C1-C12)alkylcarbonyloxy and heteroaryl;

R¹¹ is selected from the group consisting of:

H, OH, halo, C1-C4 haloalkyl, -CF₃, C1-C4 alkyl, -NH₂, C1-C4 alkoxy,

15 -NHC(=O)Me, C1-C4 alkenyl, (C1-C4)alkoxycarbonyl, (C1-C4)alkylcarbonyl, and (C1-C4)alkylcarbonyloxy;

 R^{12} is selected from the group consisting of:

H, OH, -NH₂, C1-C4 alkyl, C1-C4 alkoxy and (C1-C4)alkylcarbonyl; and R^{13} is selected from the group consisting of:

20 H, OH, halo, -NH₂, C1-C4 alkyl, C1-C4 alkoxy -N(C1-C4)alkyl.

3. The method of claim 1 with the proviso that in the compound of formula (1), if Ar^1 is

$$R^a_m \xrightarrow{Z}_X Z$$

$$Ar^1$$

wherein R^a is a noninterfering substituent; m is an integer of 0-4; each dotted line represents an optional π-bond; each Z is independently N, NR, O, S, CR or CR₂, where each R is independently H or alkyl (1-6C);

X is O, S, SO or SO₂; and

L is a flexible linker,

then Ar² is not a substituted or unsubstituted 6-membered aromatic ring; if Ar¹ is

wherein Ra is a noninterfering substituent;

n is an integer of 0 and 5; and

L is a flexible linker which does not contain nitrogen or is a constrained linker, then Ar² is not a substituted or unsubstituted phenyl or a substituted or unsubstituted naphthyl.

4. The method of claim 2 with the further proviso that in the compound of formula (1), if Ar^1 is

$$R^{a}_{m}$$
 Z Z X Ar^{1}

wherein R^a is a noninterfering substituent;

m is an integer of 0-4;

each dotted line represents an optional π -bond;

each Z is independently N, NR, O, S, CR or CR₂, where each R is independently H or alkyl (1-6C),

X is O, S, SO or SO₂; and

L is a flexible linker,

then Ar² is not a substituted or unsubstituted 6-membered aromatic ring;

if Ar1 is

wherein Ra is a noninterfering substituent;

n is an integer of 0 and 5; and

L is a flexible linker which does not contain nitrogen or is a constrained linker, then Ar² is not a substituted or unsubstituted phenyl or a substituted or unsubstituted naphthyl.

5. The method of any of claims 1-4 wherein Ar¹ is

$$R_m^a$$
 (1a)

or

$$R^a_m \longrightarrow N$$
 (2a)

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wherein each Ra is a noninterfering substituent;

m is an integer of 0-4;

the dotted line represents an optional π bond;

Z is O, S, NR or CR₂ in formula (1) or is CR in formula (2) where each R is independently H or alkyl (1-6C); and

L is a flexible conjugating or nonconjugating linker or is a constrained linker.

6. The method of claim 5 wherein L is a flexible conjugating or nonconjugating linker.

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7. The method of claim 6 wherein Z is NR.

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8. The method of claim 7 wherein Ar² is a substituted or unsubstituted aromatic system containing a 5-membered heterocycle or is

wherein R^b is a noninterfering substituent and n is an integer of 0-5; and/or
 L is -N=N-, -N=CR-, -RC=CR-, -NRNR-, -CR₂NR-, -CR₂CR₂-, -NRCO- or
 -CONR- where R is H or alkyl (1-6C); and/or
 the dotted line represents a π bond.

- 9. The method of claim 7 wherein each R^b is independently halo, OR, SR, 10 NR₂, NO, NO₂, OCF₃ or CF₃ wherein R is H or alkyl (1-6C) or R^b comprises an aromatic system.
- m is 0, and/or

 each R^b is independently OR, SR or halo;

 where n=2 and at least one R^b is OR or SR; and/or
 L is -NHCO- or -CR=CR-

The method of claim 7 wherein

- 11 The method of claim 7 wherein said compound is 59-0100, 59-103, 20 59-104, 59-105 or 59-106.
 - 12. The method of claim 6 wherein Z is S.
- 13. The method of claim 12 wherein Ar² is a substituted or unsubstituted 25 aromatic system containing a 6-membered heterocycle or is of the formula

wherein R^b is a noninterfering substituent and n is an integer of 0-5; and/or L is -N=N-, -N=CR-, -RC=CR-, -NRNR-, -CR₂NR-, -CR₂CR₂-, -NRCO- or -CONR- where R is H or alkyl (1-6C); and/or

- 5 the dotted line represents a π bond.
 - 14. The method of claim 13 wherein each R^b is independently halo, OR, SR, NR₂, NO, NO₂, OCF₃ or CF₃ wherein R is H or alkyl (1-6C) or R^b comprises an aromatic system.
- 15. The method of claim 13 wherein m is 0; and/or each R^b is independently OR, SR or halo; where n=2 and at least one R^b is OR or SR; and/or L is -NHCO- or -CR=CR-.
- 16. The method of claim 12 wherein the compound is compound number 59-002, 59-0070, 59-0072, 59-0099, the benzothiazole counterpart of 59-0104, 59-0102, 59-0144, 59-0147, 59-0149, 59-0186, 59-0187, 59-0192, 59-0193, 59-0195, 59-0197, 59-0202, 59-0204, 59-0205, 59-0206, 59-0207, 59-0208, and 59-0210.
 - 17. The method of claim 16 wherein the compound is the benzothiazole counterpart of 59-0104, or is compound number 59-0147, 59-0205 or 59-0210.
- 25 18. The method of claim 6 wherein Z is CR or CR₂.
 - 19. The method of claim 18 wherein Ar² is

wherein R^b is a noninterfering substituent and n is an integer of 0-5; and/or L is -N=N-, -N=CR-, -RC=CR-, -NRNR-, -CR₂NR-, -CR₂CR₂-, -NRCO- or -CONR- where R is H or alkyl (1-6C); and/or

the dotted line represents a π bond.

20. The method of claim 19 wherein each R^b is independently halo, OR, SR, NR₂, NO, NO₂, OCF₃ or CF₃ wherein R is H or alkyl (1-6C) or R^b comprises an aromatic system.

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- 21. The method of claim 6 wherein Z is O.
- 22. The method of claim 21 wherein Ar² is of the formula

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wherein R^b is a noninterfering substituent and n is an integer of 0-5; and/or L is -N=N-, -N=CR-, -RC=CR-, -NRNR-, -CR₂NR-, -CR₂CR₂-, -NRCO- or -CONR- where R is H or alkyl (1-6C); and/or

the dotted line represents a π bond.

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- 23. The method of claim 19 wherein each R^b is independently halo, OR, SR, NR₂, NO, NO₂, OCF₃ or CF₃ wherein R is H or alkyl (1-6C) or R^b comprises an aromatic system.
- 24. The method of claim 21 wherein the compound of formula (1) is compound number 896-5005.

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; and/or

- 25. The method of claim 5 wherein L is a constrained linker.
- 26. The method of claim 25 wherein Z is S or NR; and/or wherein L is selected from the group consisting of

wherein Ar² is

wherein R^b is a noninterfering substituent and m is 0-4.

- 27. The method of claim 25 wherein each R^b is independently halo, OR, SR, NR₂, NO, NO₂, OCF₃ or CF₃ wherein R is H or alkyl (1-6C) or comprises an aromatic system.
- The method of claim 25 wherein the compound of formula (1) is 59-0124.
 - 29. The method of any of claims 1-4 wherein Ar¹ is of the formula

$$R^a$$
 (3a)

wherein each R^a is independently a noninterfering substituent or is H; and Z is NR, S or O, wherein R is alkyl (1-6C) or H.

30. The method of claim 29 wherein Z is S; and/or wherein Ar^2 is

wherein R^b is a noninterfering substituent and n is an integer of 0-5; and/or
L is -N=N-, -N=CR-, -RC=CR-, -NRNR-, -CR₂NR-, -CR₂CR₂-, -NRCO- or
-CONR- where R is H or alkyl (1-6C); and/or

the dotted line represents a π bond; and/or
each R^b is independently halo, OR, SR, NR₂, NO, NO₂, OCF₃ or CF₃ wherein
R is H or alkyl (1-6C) or comprises an aromatic system.

31. The method of any of claims 1-4 wherein Ar¹ is

$$R^a_m$$
 (4a)

wherein Ra is a noninterfering substituent;

m is an integer of 0-4;

each dotted line represents an optional π -bond;

each Z is independently N, NR, CR or CR₂, where each R is independently H or alkyl (1-6C) with the proviso that at least one Z is N or NR.

The method of claim 31 wherein Ar¹ is

$$R^{a}_{m}$$
 (5a)

33. The method of claim 31 wherein Ar₂ is

$$R^{b}_{n}$$
 R^{b}_{m} R^{b}_{m} (vi) or N (via)

wherein each R^b is independently a noninterfering substituent, and n is 0-5 and m is 0-4; and/or

- L is -N=N-, -RC=CR-, -RC=N-, -NRCO-, -NRCR₂-, -NRCR₂CR₂-, -NRCR₂CO-, -NRNR-, -CR₂CR₂-, -NRCR₂CR₂NR-, -NRCR=CRNR- or -NRCOCR₂NR-.
- 34. The method of claim 33 wherein each R^b is independently halo, OR, SR, NR₂, NO, NO₂, OCF₃ or CF₃ wherein R is H or alkyl (1-6C) or R^b comprises an aromatic system.
- 35. The method of claim 32 wherein each R^b is NR₂ or OR and m and n are 0, 1 or 2; and/or
 L is -CR=CR₋,-N=N₋ or -NRCO₋
 - 36. The method of claim 35 wherein the compound of formula (1) is 59-0030, 59-0078, 59-0091, 59-0093, 59-0150, 50-0197, 59-0198, 59-0199 or 59-0480.

37. The method of claim 31 wherein Ar_2 is substituted or unsubstituted quinolyl or naphthyl of the formula

wherein each R^b is a noninterfering substituent and m is 0-4.

38. The method of claim 37 wherein L is -N=N-, -RC=CR-, -RC=N-,
-NRCO-, -NRCR₂-, -NRCR₂CR₂-, -NRCR₂CO-, -NRNR-, -CR₂CR₂-,
-NRCR₂CR₂NR-, -NRCR=CRNR- or -NRCOCR₂NR-; and/or

wherein each R^b is independently halo, OR, SR, NR₂, NO, NO₂, OCF₃ or CF₃ wherein R is H or alkyl (1-6C) or R^b comprises an aromatic system and m is 0, 1 or 2.

- 10 39. The method of claim 38 wherein the compound of formula (1) is 59-0089, 59-0090, 59-0092 or 59-0094.
 - 40. The method of claim 31 wherein Ar¹ is

$$R^a_m$$
 (6a) or N (7a) or N (8a)

wherein each R^a is a noninterfering substituent and m is 0-4.

41. The method of claim 40 wherein L is -N=N-, -RC=CR-, -RC=N-, -NRCO-, -NRCR₂-, -NRCR₂CR₂-, -NRCR₂CO-, -NRNR-, -CR₂CR₂-, -NRCR₂CR₂-, -NRCR₂CR₂NR-, -NRCR=CRNR- or -NRCOCR₂NR-; and/or

 Ar^2 is

wherein R^b is a noninterfering substituent and n is an integer of 0-5; and/or wherein each R^b is independently halo, OR, SR, NR₂, NO, NO₂, OCF₃ or CF₃ wherein R is H or alkyl (1-6C) or R^b comprises an aromatic system.

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- 42. The method of claim 41 wherein the compound of formula (1) is 59-203, 59-285 or 59-286.
 - 43. The method of claim 31 wherein L is a constrained linker.

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44. The method of any of claims 1-4 wherein Ar¹ is

$$\begin{array}{c|c}
R^{a}_{m} & z = z \\
z & z \\
z - z
\end{array} (9a)$$

wherein each R^a is independently a noninterfering substituent; m is an integer of 0-4;

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- each Z is independently N or CR, where R is H or alkyl (1-6C), with the proviso that at least one Z must be N and at least one Z must be CR.
- 45. The method of claim 44 wherein L is a flexible conjugating or nonconjugating linker; and/or
- wherein Ar^2 is

$$R^{b}_{n}$$
 (v) or $Z = Z$ (vi)

wherein each R^b is independently a noninterfering substituent, and

in (vi) each Z is independently N or CR, where R is H or alkyl (1-6C), with the proviso that at least one Z must be a N and at least one Z must be CR.

46. The method of claim 45 wherein the compound of formula (1) is of the formula

$$R^{a}_{m}$$
 or R^{b}_{n}

- 47. The method of claim 46 wherein L is -N=N-, -RC=CR-, -RC=N-, -NRCO-, -NRCR₂-, -NRCR₂CR₂-, -NRCR₂CO-, -NRNR-, -CR₂CR₂-,
- -NRCR₂CR₂NR-, -NRCR=CRNR- or -NRCOCR₂NR-; and/or wherein each R^a and R^b is independently halo, OR, SR, NR₂, NO, NO₂, OCF₃ or CF₃ wherein R is H or alkyl (1-6C) or R^b comprises an aromatic system and each m and n is independently 0, 1 or 2.
- The method of claim 47 wherein L is -NHCR₂CR₂NH-, m is 1 and R² is CF₃ para to L.
 - 49. The method of claim 48 wherein the compound of formula (1) is 59-0145, 59-0450, 59-0459 or 59-0483.
 - 50. The method of any of claims 1-4 wherein Ar¹ is

wherein each R^a is a noninterfering substituent; and n is an integer of 0 and 5, and

wherein L is a flexible linker that contains at least one nitrogen; and/or

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wherein Ar² is of the formula

and L is -N=N-, -RC=CR-, -RC=N-, -NRCO-, -NRCR₂-, -NRCR₂CR₂-,
-NRCR₂CO-, -NRNRCR₂CR₂-, -NRNRCR=CR-, -NRNRCOCR₂-,
-NRNRCOCR=CR-, -NRNRCSCR₂-, -NRNRCSCR=CR-, -NRNRCONR-,
-NRNRCSNR-, -NRNR-, -CR₂CR₂-, -NRCR₂CR₂NR-, -NRCR=CRNR- or
-NRCOCR₂NR-.

- 51. The method of claim 50 wherein each R^b is independently halo, OR,

 SR, NR₂, NO, NO₂, OCF₃ or CF₃ wherein R is H or alkyl (1-6C) or R^b comprises an aromatic system.
- 52. The method of claim 50 wherein L is -CR=CRCONRNR-,
 -CR=CRCSNRNR-, -CR₂CONRNR- -CR₂CSNRNR-, -NRNRCONR- or
 15 -NRNRCSNR- and/or
 R^b is -NR₂ and n=1 wherein R^b is in the para position.
 - 53. The method of claim 50 wherein R^a is -COOR and m is 1.
- 20 54. The method of claim 52 wherein the compound of formula (1) is 59-0045, 59-0095, 59-0096, 59-0097 or 59-0098.
- 55. A pharmaceutical composition for use in a method to treat a condition in a vertebrate animal characterized by a deficiency in, or need for, bone growth
 replacement and/or an undesirable level of bone resorption which composition contains a pharmaceutically acceptable excipient and an effective amount of a compound of the formula set forth in any preceding claim.

56. A compound for use in preparing a composition for use in the treatment of a condition in a vertebrate animal characterized by a deficiency in, or need for, bone growth replacement and/or an undesirable level of bone resorption which method comprises administering said composition to a vertebrate subject, said compound set forth in any preceding claim.

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Ar ¹ - lini 1.5 -	(I)	
Ar ¹	Ar ²	
contains 5-membered heterocycle	substituted or unsubstituted benzene	II-A
contains 5-membered heterocycle	substituted or unsubstituted naphthalene	II-B
contains 5-membered heterocycle	contains 6-membered heterocycle	II-C
contains 5-membered heterocycle	contains 5-membered heterocycle	II-D
contains 6-membered heterocycle	substituted or unsubstituted benzene	II-E
contains 6-membered heterocycle	substituted or unsubstituted naphthalene	II-F
contains 6-membered heterocycle	contains 6-membered heterocycle	II-G
substituted or unsubstituted naphthalene	substituted or unsubstituted benzene	п-н
substituted or unsubstituted naphthalene	substituted or unsubstituted naphthalene	II-I
substituted or unsubstituted benzene	substituted or substituted or	

Figure 1

	CELLS		10/1/96						
x 10° C	ells/weil	READ 1	READ 2	AVERAGE	INDUCTION	AVE-BASAL	9/ 14A Y		
S-8	135.000		0 22	0.22	0 16:		-17 90		
	31 250		4 44		3.49	3.00	54.26		
	9.766			6 72	5.59	5.52			
	3.052		4.88		3.95	3.55	64 22		 ···
	0 954		3 16		2.61	1.94	35.12	 ·	
	J 298	2.75	2 59		2.221		26.581		
	0.093		2.34	2.07			15.77	· -	
	0.029	1 56	•.7:	: 63	1.36	0.43	7.80		
	0.0091	1.45	1.42	1 44	1.19	0.23	4.21!		
	0.0028	1 28	1.37	1.33	1.10	0.12	2.251		
	0.0000		1.30					·	
	J.CC00	1.20	• 30	1 10					
		AVERAGE		1 20			<u>-</u>		
% HAX	50.00 							<u>.</u>	◆ - OS- s
•	20 00 - 0 00 - 0 00	00	1	0.10	1.00	10.0	•	100.00	
	·zo.00 :			uAA	O3-4			•	

Figure 2

NNC#	MOLWEIGHT	Concentration	-% Response i
	1		
_]	1 1
	1	!	
Î			
'			1 1
50-0194	430.33	 	1 1
50-0194		100.00 uM	-19.1901
	ĺ	31.25luM	32.4501
	<u>:</u>	9.77 uM	-14.240
	<u> </u>	3.05 uM	-11.330
		i 953.67 nM	-12.790
	<u> </u>	298.02 nM	-13.450
	i	93.13 nM	-12.290
	1	29.10InM	-9.440 -6.450
	i	9.09 nM 2.84 nM	-8.130
	1	888.18 pM	-3.320
		· vvv. reipm	1 1
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	·	<u> </u>	
50-0195	275.36		<u> </u>
50-0195	 	100.00 uM	4.630i 16.790i
	- 	31.25 uM 9.77 uM	· 16.7901 62.830
	-	3.05 uM	102.720
		953.67 InM	60.8601
		298.02 nM	32.4501
	1	93 13 nM	19.3401
		29.10 nM	17.2201
·	1	9.09 nM	5.640
		2.841nM	4.8401
		888.18IpM	5.640!
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50-0196	276.3		!
50-0196		100.001uM	-16.210
		31.25luM	-8.550
	<u> </u>	9.771uM	: 11.620 : 27.7901
		3.05 uM 953.67 nM	18.390
		298.02 nM	6.230
		93.13 nM	12.420
		29.101nM	12.630
		9.09InM	6.5901
		2.841nM	7.970
	<u>-</u> -	888.181pM	5.0601

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50-0197	274,37		
50-0197	! 2/4.3/1	100.00114	
		100.00 uM	-18.250
		31.25 uM 9.77 uM	-14.980!
		3.051uM	4.040;
		953.67 InM	93.790
		298.02 nM	242.9201
	1	93.13 nM	195.890
	1	29.10 nM	115.320
	i i	9.09 nM	85.630
	1	2.84 nM	54.380
		888.18 pM	33.180
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9-0008	254.32		
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<del>3-0</del> 019	59-0019		
-0019	1	100.00 tuM	-22.240
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	<del> </del>	31.25 uM	-22.670
		31.25 uM 9.77 uM	-22.670    -17.470
		31.25 uM 9.77 uM 3.05 uM	-22.670    -17.470    74.490
		31.25 uM 9.77 uM 3.05 uM 953.67 inM	-22.670    -17.470    74.490    198.080
		31.25 uM 9.77 uM 3.05 luM 953.67 inM 298.02 inM	-22.670    -17.470    74.490    198.080    258.340
		31.25 uM 9.77 uM 3.05 uM 953.67 inM 298.02 inM 93.13 inM	: -22.670    -17.470    74.490   : 198.080   : 258.340    225.350
	i	31.25 uM 9.77 uM 3.05 uM 953.67 inM 298.02 inM 93.13 inM 29.10 inM	-22.670    -17.470    74.490    198.080    258.340    225.350    75.220
		31.25 uM 9.77 uM 3.05 uM 953.67 inM 298.02 inM 93.13 inM 29.10 inM 9.09 inM	-22.670    -17.470    74.490    198.080    258.340    225.350    75.220    24.030
		31.25 uM 9.77 uM 3.05 uM 953.67 inM 298.02 inM 93.13 inM 29.10 inM 9.09 inM 2.84 inM	-22.670    -17.470    74.490    198.080    258.340    225.350    75.220    24.030    34.480
		31.25 uM 9.77 uM 3.05 uM 953.67 inM 298.02 inM 93.13 inM 29.10 inM 9.09 inM	-22.670    -17.470    74.490    198.080    258.340    225.350    75.220    24.030
		31.25 uM 9.77 uM 3.05 uM 953.67 inM 298.02 inM 93.13 inM 29.10 inM 9.09 inM 2.84 inM	-22.670    -17.470    74.490    198.080    258.340    225.350    75.220    24.030    34.480
		31.25 uM 9.77 uM 3.05 uM 953.67 inM 298.02 inM 93.13 inM 29.10 inM 9.09 inM 2.84 inM	-22.670    -17.470    74.490    198.080    258.340    225.350    75.220    24.030    34.480
		31.25 uM 9.77 uM 3.05 uM 953.67 inM 298.02 inM 93.13 inM 29.10 inM 9.09 inM 2.84 inM	-22.670    -17.470    74.490    198.080    258.340    225.350    75.220    24.030    34.480
		31.25 uM 9.77 uM 3.05 uM 953.67 inM 298.02 inM 93.13 inM 29.10 inM 9.09 inM 2.84 inM	-22.670    -17.470    74.490    198.080    258.340    225.350    75.220    24.030    34.480
		31.25 uM 9.77 uM 3.05 uM 953.67 inM 298.02 inM 93.13 inM 29.10 inM 9.09 inM 2.84 inM	-22.670    -17.470    74.490    198.080    258.340    225.350    75.220    24.030    34.480
		31.25 uM 9.77 uM 3.05 uM 953.67 inM 298.02 inM 93.13 inM 29.10 inM 9.09 inM 2.84 inM	-22.670    -17.470    74.490    198.080    258.340    225.350    75.220    24.030    34.480
-0020		31.25 uM 9.77 uM 3.05 uM 953.67 inM 298.02 inM 93.13 inM 29.10 inM 9.09 inM 2.84 inM	-22.670    -17.470    74.490    198.080    258.340    225.350    75.220    24.030    34.480
-0020		31.25 uM 9.77 uM 3.05 uM 953.67 inM 298.02 inM 93.13 inM 29.10 inM 9.09 inM 2.84 inM 888.18 ipM	-22.670  -17.470  74.490  198.080  258.340  225.350  75.220  24.030  34.480  -3.740
-0020	286.73	31.25 LM 9.77 LM 3.05 LM 953.67 InM 298.02 InM 93.13 InM 29.10 InM 9.09 InM 2.84 InM 888.18 IpM	-22.670  -17.470  -74.490  -198.080  -258.340  -225.350  -75.220  -24.030  -34.480  -3.740
0020 -0020	286.73	31.25 uM 9.77 uM 3.05 uM 953.67 inM 298.02 inM 93.13 inM 29.10 inM 9.09 inM 2.84 inM 888.18 ipM	-22.670  -17.470  74.490  198.080  258.340  225.350  75.220  24.030  34.480  -3.740
-0020	266.73	31.25 uM 9.77 uM 3.05 uM 953.67 inM 298.02 inM 93.13 inM 29.10 inM 9.09 inM 2.84 inM 888.18 ipM	-22.670  -17.470  74.490  198.080  258.340  225.350  75.220  24.030  34.480  -3.740   -18.510  -16.040  -0.270
-0020	266.73	31.25 uM 9.77 uM 3.05 uM 953.67 inM 298.02 inM 93.13 inM 29.10 inM 9.09 inM 2.84 inM 888.18 ipM 100.00 uM 31.25 uM 9.77 uM 3.05 uM	-22.670  -17.470  74.490  198.080  258.340  225.350  75.220  24.030  34.480  -3.740   -16.510  -16.040  -0.270
-0020	266.73	31.25 uM 9.77 uM 3.05 uM 953.67 inM 298.02 inM 93.13 inM 29.10 inM 9.09 inM 2.84 inM 888.18 ipM	-22.670  -17.470  74.490  198.080  258.340  225.350  75.220  24.030  34.480  -3.740   -18.510  -16.040  -0.270

	29.10 nM	37.870:
	9.09 nM	24.8201
<del></del>	2.84 nM	20.500
	1 688.181pM	13.310

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0-0021	284.72		100000
9-0021		100.001uM 31.251uM	-16.310i -12.850i
		9.77 luM	84.1301
	<del></del>	3.05 luM	1 89.9401
	1	953.67 inM	65.7501
		298.021nM	33.9401
!	•	93.13 nM	22.5601
	<u> </u>	29.10inM	25.0201
		9.091nM 2.841nM	1 13.910 1 33.2701
		588.181pM	15.5001
	<del></del>	300.101pm	1 13.330
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9-0022	268.37		<u> </u>
9-0022		100.001uM	7.250:
		31.25\uM 9.77\uM	: -2.070. ! '-0.2701
	<del></del>	3.05luM	4.3901
	<del></del>	953.67 inM	i 3.060
		298.021nM	-1.8001
:	i	93.13 nM	i -0.2001
i	1	29.10inM	i -3.2701
	1	9.091nM	1 1.1301
		2.84 inM	2.5901
	<u></u>	688.18ipM	2.4601
i			
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59-0023	239.28		
59-0023	<u> </u>	100.00 uM	-12.720! : 33.140!
	1	31.25(uM 9.77!uM	33.1401 56.5001
1		3.051uM	29.5501
<u> </u>	· · · · · · · · · · · · · · · · · · ·	953.67 nM	25.3601
	<u>-</u>	298.02 inM	1 15.7001
	<u>-</u>	93.13InM	7.3801
		29.10InM	-9.7101
:	!	9.09InM	1.0001
		2.841nM	4,5201
	<del></del>	888.181pM	-0 010

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59-0024	220.28		
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59-0025		.	
59-0025	224.31		<u> </u>
	<del></del>	100.001uM	25.5901
	<del></del>	31.25 uM 9.77 uM	14.1501
		3.05 uM	50.5901
		953.67 nM	38.9001
	1	298.02 nM	28.530
		93.13 nM	19.660
		29.10 nM	17.490
		9.09 nM	-0.6001
<del></del>		2.84 inM	-4.1901
<del></del>		888.18 pM	4.670i
		+	ļ <u> </u>
			1 1
59-0026 59-0026	248.29		
39-0026		100.001uM	-29.8301
		31.25 UM	i -9.4401
		9.771uM 3.051uM	i -10.470l
		953.67 nM	1 107.760
	<del></del>	298.02 nM	107.760
	<del></del>	93.13InM	36.8501
		29.10 nM	26.720
		9.09 nM	8.520
		2.84 nM	-1.240
		888.18 pM	4.020

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59-0027	250.30	Ţ		
59-0027	230.301			
	<del></del>	100.00 uM	89.8101	
		31.25 JuM	54.6701	
		9.77 uM	44.9401	
		3.05 uM	23.7801	
		953.67InM	8.3801	
	<del></del>	298.02 InM	6.330	
· <del>  </del>		93.13 nM	. 7.360	
		29.10 nM	3.3801	
		9.09 nM	-1.6201	
	<u></u>	2.84 nM	-3.570	
	<u>_</u>	888.18 pM	-0.7201	
59-0028	226.28			
59-0028	1	100.00 luM	26.780	
	<del></del>	31.25 uM	-26.7501 -16.7401	
		9.77 uM	29.5501	<del> </del>
	<del></del>	3.05 uM	100.580)	
		953.67 nM	54.940	
		298.02 inM	31.3401	<b></b> -i
		93.13inM	7.500	——
	<u>-</u> <u>-</u>	29.10 nM		
	<del></del>	9.09InM		
		2.84 nM	7.8801	
	<del></del>	888.16 pM	3.1401	
		COO. TO IDAN	4 670:	

59-0029 249.27 59-0029 100.00 uM -15.160   31.25 uM 41.940   9.77 uM 36.630   3.05 uM 7.120   953.67 nM 21.880
59-0029 100.00 uM -15.1601 31.25 uM 41.940 9.77 uM 36.6301 3.05 uM 7.120
59-0029 100.00 uM -15.1601 31.25 uM 41.940 9.77 uM 36.6301 3.05 uM 7.120
59-0029 100.00 uM -15.1601 31.25 uM 41.940 9.77 uM 36.6301 3.05 uM 7.120
59-0029 100.00 uM -15.1601 31.25 uM 41.940 9.77 uM 36.6301 3.05 uM 7.120
59-0029 100.00 uM -15.1601 31.25 uM 41.940 9.77 uM 36.6301 3.05 uM 7.120
59-0029 100.00 uM -15.1601 31.25 uM 41.940 9.77 uM 36.6301 3.05 uM 7.120
59-0029 100.00 uM -15.1601 31.25 uM 41.940 9.77 uM 36.6301 3.05 uM 7.120
59-0029 100.00 uM -15.1601 31.25 uM 41.940 9.77 uM 36.6301 3.05 uM 7.120
59-0029 100.00 uM -15.1601 31.25 uM 41.940 9.77 uM 36.6301 3.05 uM 7.120
59-0029 100.00 uM -15.1601 31.25 uM 41.940 9.77 uM 36.6301 3.05 uM 7.120
31.25 uM 41.940 9.77 uM 36.630 3.05 uM 7.120
9.77 uM 36.6301 3.05 uM 7.120
3.05 uM : 7.120
3.05 LW . 7.120
063.67 pt
953.571nM : 21.8801
298.02 nM 15.540
93.13 nM 1.810
29.10 nM 1.370
2.00111111 - 3.2301
888.181pM : 9.0401
59-0030 A
59-0030 A 233.28
59-0030 A . 100.00 uM -27.970
59-0030 A .100.00 uM -27.970
59-0030 A .100.00 uM -27.970
59-0030 A .100.00 uM -27.970
59-0030 A 100.00 luM -27.9701 31.25 luM -22.8301 9.77 luM -5.4201 3.05 luM 57.2801 953.67 lnM 72.6201
59-0030 A .100.00 uM27.9701 31.25 uM22.8301 9.77 uM5.4201 3.05 uM .57.2801 953.67 nM .72.6201
59-0030 A 100.00 luM -27.9701 31.25 luM -22.8301 9.77 luM -5.4201 3.05 luM 57.2801 953.67 lnM 72.6201 298.02 lnM 53.0001
59-0030 A 100.00 luM -27.9701 31.25 luM -22.8301 9.77 luM -5.4201 3.05 luM 57.2801 953.67 lnM 72.6201 298.02 lnM 53.0001 93.13 lnM 29.9901
59-0030 A 100.00 luM -27.9701 31.25 luM -22.8301 9.77 luM -5.4201 3.05 luM 57.2801 953.67 lnM 72.6201 298.02 lnM 53.0001 93.13 lnM 29.990: 29.10 lnM 14.630;
59-0030 A 100.00 luM -27.9701 31.25 luM -22.8301 9.77 luM -5.4201 3.05 luM 57.2801 953.67 lnM 72.6201 298.02 lnM 53.0001 93.13 lnM 29.990; 29.10 lnM 14.630; 9.09 lnM 3.8701
59-0030 A 100.00 luM -27.9701 31.25 luM -22.8301 9.77 luM -5.4201 3.05 luM 57.2801 953.67 lnM 72.6201 298.02 lnM 53.0001 93.13 lnM 29.990; 29.10 lnM 14.630; 9.09 lnM 3.8701 2.84 lnM 6.970;
59-0030 A 100.00 luM -27.9701 31.25 luM -22.8301 9.77 luM -5.4201 3.05 luM 57.2801 953.67 lnM 72.6201 298.02 lnM 53.0001 93.13 lnM 29.990; 29.10 lnM 14.630; 9.09 lnM 3.8701
59-0030 A 100.00 luM -27.9701 31.25 luM -22.8301 9.77 luM -5.4201 3.05 luM 57.2801 953.67 lnM 72.6201 298.02 lnM 53.0001 93.13 lnM 29.990; 29.10 lnM 14.630; 9.09 lnM 3.8701 2.84 lnM 6.970;
59-0030 A 100.00 luM -27.9701 31.25 luM -22.8301 9.77 luM -5.4201 3.05 luM 57.2801 953.67 lnM 72.6201 298.02 lnM 53.0001 93.13 lnM 29.990; 29.10 lnM 14.630; 9.09 lnM 3.8701 2.84 lnM 6.970;
59-0030 A 100.00 luM -27.9701 31.25 luM -22.8301 9.77 luM -5.4201 3.05 luM 57.2801 953.67 lnM 72.6201 298.02 lnM 53.0001 93.13 lnM 29.990; 29.10 lnM 14.630; 9.09 lnM 3.8701 2.84 lnM 6.970;
59-0030 A 100.00 luM -27.9701 31.25 luM -22.8301 9.77 luM -5.4201 3.05 luM 57.2801 953.67 lnM 72.6201 298.02 lnM 53.0001 93.13 lnM 29.990; 29.10 lnM 14.630; 9.09 lnM 3.8701 2.84 lnM 6.970;
59-0030 A 100.00 luM -27.9701 31.25 luM -22.8301 9.77 luM -5.4201 3.05 luM 57.2801 953.67 lnM 72.6201 298.02 lnM 53.0001 93.13 lnM 29.990; 29.10 lnM 14.630; 9.09 lnM 3.8701 2.84 lnM 6.970;
59-0030 A 100.00 luM -27.9701 31.25 luM -22.8301 9.77 luM -5.4201 3.05 luM 57.2801 953.67 lnM 72.6201 298.02 lnM 53.0001 93.13 lnM 29.990; 29.10 lnM 14.630; 9.09 lnM 3.8701 2.84 lnM 6.970;
59-0030 A 100.00 luM -27.9701 31.25 luM -22.8301 9.77 luM -5.4201 3.05 luM 57.2801 953.67 lnM 72.6201 298.02 lnM 53.0001 93.13 lnM 29.990; 29.10 lnM 14.630; 9.09 lnM 3.8701 2.84 lnM 6.970;
59-0030 A 100.00 luM -27.970 l 31.25 luM -22.830 l 9.77 luM -5.420 l 3.05 luM 57.280 l 953.67 lnM 72.620 l 298.02 lnM 53.000 l 93.13 lnM 29.990 l 29.10 lnM 14.630 l 9.09 lnM 3.870 l 2.84 lnM 6.970 l 888.18 lpM 1.810 l
100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   1
59-0030 A 100.00 luM -27.970 l 31.25 luM -22.830 l 9.77 luM -5.420 l 3.05 luM 57.280 l 953.87 lnM 72.620 l 298.02 lnM 53.000 l 93.13 lnM 29.990 l 29.10 lnM 14.630 l 9.09 lnM 3.870 l 2.84 lnM 6.970 l 888.18 lpM 1.810 l 59-0031 231.30 l
59-0030 A 100.00 luM -27.970 l 31.25 luM -22.830 l 9.77 luM -5.420 l 3.05 luM 57.280 l 953.67 lnM 72.620 l 298.02 lnM 53.000 l 93.13 lnM 29.990 l 29.10 lnM 14.630 l 9.09 lnM 3.870 l 2.84 lnM 6.970 l 888.18 lpM 1.810 l 59-0031 231.30 l 100.00 luM -25.790 l 31.25 luM -17.810 l
59-0030 A 100.00 luM -27.970 l 31.25 luM -22.830 l 9.77 luM -5.420 l 3.05 luM 57.280 l 953.87 lnM 72.620 l 298.02 lnM 53.000 l 93.13 lnM 29.990 l 29.10 lnM 14.630 l 9.09 lnM 3.870 l 2.84 lnM 6.970 l 888.18 lpM 1.810 l 59-0031 231.30 l
59-0030 A 100.00 luM -27.970 l 31.25 luM -22.830 l 9.77 luM -5.420 l 3.05 luM 57.280 l 953.67 lnM 72.620 l 298.02 lnM 53.000 l 93.13 lnM 29.990 l 29.10 lnM 14.630 l 9.09 lnM 3.870 l 2.84 lnM 6.970 l 888.18 lpM 1.810 l 59-0031 231.30 l
100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   1
59-0030 A
59-0030 A  100.00 uM  -27.970  31.25 uM  -22.8301  9.77 uM  -5.4201  3.05 uM  57.2801  953.67 nM  72.6201  298.02 nM  14.6301  9.09 nM  3.8701  29.0031  231.30  231.30  231.30  231.30  231.30  231.30  231.30  231.30  231.30  231.30  231.30  231.30  231.30  231.30  331.25 uM  -17.8101  9.77 uM  20.8401  3.05 uM  87.3801  953.67 nM  49.3201  298.02 nM  143.1101
59-0030 A 100.00 I
100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   1
59-0030 A 100.00 iuM -27.970   31.25 iuM -22.830   9.77 iuM -5.420   3.05 iuM 57.280   9.77 iuM 53.000   93.67 iuM 72.820   93.67 iuM 72.820   93.13 iuM 29.990   93.13 iuM 29.990   93.13 iuM 29.990   93.13 iuM 29.990   93.13 iuM 6.970   93.64 iuM 6.970   93.64 iuM 6.970   93.64 iuM 6.970   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM 18.00   93.65 iuM
100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   100.00   1

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59-0032	348.30		
59-0032	248.29	400.001.44	
	<del> </del>	100.001uM	-7.7801
A-F		31.25(uM 9.77(uM	40.7501
	<del> </del>	3.05 luM	42.8201
	i -	953.67 nM	25.7001
	<del>_</del>	298.02 nM	31.170 34.410
		93.13 nM	
	i i	29.10InM	3.570 4.320
	i i	9.09 nM	-10.000
		2.84InM	5.650
		888.18 pM	11.9901
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59-0033	248.29		1 1
59-0033		100.00 uM	-28.1801
		31.25/uM	-11.590
		9.77 uM	55.3001
		3.05 UM	49.7101
		953.67 InM	47.4101
· · · · · · · · · · · · · · · · · · ·		298.02 InM	0.250
		93.13 nM	7.980!
		29.10 nM	-8.9401
		9.091nM	-7.6301
		2.841nM	-0.4001
	1	558.181pM	-5.9801
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59-0034	268.34		
59-0034		100.001uM	-28.511
		31.25luM	241
		9.77 luM	73.581
l		3.05 uM	37.91
		953.67 InM	20.09
		298.021nM	16.87
		93.131nM	15.23
		29.10 nM	28.83
		9.091nM	9.08
		2.84 InM	23.021
		888.181pM	-0.32!

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59-0035	291.36		:
59-0035		100.001uM	-14.92!
	1	31.25 uM	29.17
		9.771uM	15.871
·		3.05iuM	18.81
<u> </u>	1	953.67 InM	3.861
		298.02 inM	6.15
<u> </u>		93.13InM	3.221
	<u></u>	29.10inM	-10.031
		9.09 nM	15.58
<u> </u>		2.84 nM	-3.561
<u> </u>	<u></u>	888.181pM	: -7 131
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59-0036	262.31		<u>:</u>
59-0036	1	100.00 luM	-0.98
		31.25luM	-3.25
<del></del>		9.77 uM	-4.541
	<del></del>	3.051uM	-1.95i
	<u>_</u>	953.671nM	0.321
	<u>:</u> !	298.021nM	-6.49!
<del></del>	<del></del>	93.13InM	-17.19!
	<u> </u>	29.10InM	-0.66
<u> </u>		9.09InM	-5.521
	<u> </u>	2.841nM	-9.41
	<u> </u>	888.18IpM	-16.53·
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59-0037	308.00		
59-0037		100.001uM	-10 69:
	<u> </u>	31.25luM	-11.99:
		9.77 iuM	-10.03
	!	3.051uM	-19.11:
	<u>_</u> <u>l</u>	953.67 inM	-9.41
!	<u> </u>	298.02 inM	: 2,271
i,		93.13InM	-2.9i
	:	29.10InM	-10.69!
		9.091nM	2.59
		2.841nM	0.661
	<u>-</u> :	888.181pM	-= -2.59i

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59-0038	291.36	[	!
59-0038		100.001uM	-23.430
<u> </u>	1	31.251uM	-8.3901
		9.771uM	-0.1001
<del></del>		3.05 uM	-2.8601
		953.67 InM	-2.240
	<u> </u>	298.02 inM	3.9001
		93.13InM	6.350
	<del>!</del> -	29.10InM	1.150
	<del></del>	9.09 nM	6.960
	<del></del>	2.841nM	4.3901
<u> </u>	<del></del>	888.161pM	-0.3801
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59-0039	312.35		<u>i</u> 1
59-0039	<u> </u>	100.001uM	14.170(
		31.25 uM	7.620
	<u> </u>	9.77 uM	1.9401
		3.05 iuM	-3.1401
		953.67 inM	-7.770i
1		298.02 tnM 93.13 lnM	-5.9801
		29.10InM	-8.820:
		9.091nM	-2.390!
		2.84 nM	-16.580 i
	· · · · · · · · · · · · · · · · · · ·	888.181pM	-4 4801 -0.450:
		OGG. FOIDIN	-0.430:
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59-0040	290.37		• 1
59-0040		100.001uM	-20 400
		31:25(uM	-17,310;
<u> </u>		9.77 LUM	-8.110
		3.051uM	32.180
<u> </u>		953.67 inM	36.1801
		298.02!nM	17.4401
	<u> </u>	93.13InM	2.040
<u> </u>	· !	29.10 nM	10.350
		9.09inM 2.84inM	≔6.070 1
		888.181pM	6.9601
		300.1010M	13,4401

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59-0041	501.90		
59-0041	i	100.001uM	-18.37:
<u></u>		31.251uM	-17.331
		9.77 luM	-5.111
<u> </u>		3.051uM	3.311
<u> </u>	i_	953.67InM	-0.771
<u> </u>		298.021nM	-1.56
	<u> </u>	93.13 nM	3.55
		29.10 nM	-11.24
	·	9.09 nM	0.25
		2.84 InM	-0.27
	<u> </u>	888.18 pM	2.02
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59-0042		,	
59-0042	281.36		
33-00-2	l l	100.00 uM	163.51
			103.51
		31.25 JuM	-7.671
		31.25 uM 9.77 uM	-7.67! 9.41!
		31.25 uM 9.77 uM 3.05 uM	-7.67: 9.41: 0.75i
		31.25 luM 9.77 luM 3.05 luM 953.67 lnM	-7.67: 9.41: 0.75: 6.11:
		31.25 uM 9.77 uM 3.05 uM 953.67 nM 298.02 nM	-7.67: 9.41: 0.75: 6.11: 3.82:
		31.25 uM 9.77 uM 3.05 uM 953.67 nM 298.02 nM 93.13 nM	-7.67; 9.41; 0.75; 6.11; 3.82; 2.54;
		31.25 uM 9.77 uM 3.05 uM 953.67 nM 298.02 nM 93.13 nM 29.10 nM	-7.67; 9.41; 0.75; 6.11; 3.82; 2.54; 4.07;
		31.25 uM 9.77 uM 3.05 uM 953.67 nM 298.02 nM 93.13 nM 29.10 nM 9.09 nM	-7.67; 9.41; 0.75; 6.11; 3.82; 2.54; 4.07; -9.73;
		31.25 uM 9.77 uM 3.05 uM 953.67 nM 298.02 nM 93.13 nM 29.10 nM 9.09 nM 2.84 nM	-7.67; 9.41; 0.75; 6.11; 3.82; 2.54; 4.07; -9.73; -0.02;
		31.25 uM 9.77 uM 3.05 uM 953.67 nM 298.02 nM 93.13 nM 29.10 nM 9.09 nM	-7.67; 9.41; 0.75; 6.11; 3.82; 2.54; 4.07; -9.73;
		31.25 uM 9.77 uM 3.05 uM 953.67 nM 298.02 nM 93.13 nM 29.10 nM 9.09 nM 2.84 nM	-7.67; 9.41; 0.75; 6.11; 3.82; 2.54; 4.07; -9.73; -0.02;
		31.25 uM 9.77 uM 3.05 uM 953.67 nM 298.02 nM 93.13 nM 29.10 nM 9.09 nM 2.84 nM	-7.67; 9.41; 0.75; 6.11; 3.82; 2.54; 4.07; -9.73; -0.02;
O THE O		31.25 uM 9.77 uM 3.05 uM 953.67 nM 298.02 nM 93.13 nM 29.10 nM 9.09 nM 2.84 nM	-7.67; 9.41; 0.75; 6.11; 3.82; 2.54; 4.07; -9.73; -0.02;
		31.25 uM 9.77 uM 3.05 uM 953.67 nM 298.02 nM 93.13 nM 29.10 nM 9.09 nM 2.84 nM	-7.67; 9.41; 0.75; 6.11; 3.82; 2.54; 4.07; -9.73; -0.02;
		31.25 uM 9.77 uM 3.05 uM 953.67 nM 298.02 nM 93.13 nM 29.10 nM 9.09 nM 2.84 nM	-7.67; 9.41; 0.75; 6.11; 3.82; 2.54; 4.07; -9.73; -0.02;
		31.25 uM 9.77 uM 3.05 uM 953.67 nM 298.02 nM 93.13 nM 29.10 nM 9.09 nM 2.84 nM	-7.67; 9.41; 0.75; 6.11; 3.82; 2.54; 4.07; -9.73; -0.02;
		31.25 uM 9.77 uM 3.05 uM 953.67 nM 298.02 nM 93.13 nM 29.10 nM 9.09 nM 2.84 nM	-7.67; 9.41; 0.75; 6.11; 3.82; 2.54; 4.07; -9.73; -0.02;
	1	31.25 uM 9.77 uM 3.05 uM 953.67 nM 298.02 nM 93.13 nM 29.10 nM 9.09 nM 2.84 nM	-7.67; 9.41; 0.75; 6.11; 3.82; 2.54; 4.07; -9.73; -0.02;
59-0043 59-0043	280.29	31.25 LLM 9.77 LLM 3.05 LLM 953.67 LLM 298.02 LLM 93.13 LLM 29.10 LLM 9.09 LLM 2.84 LLM 888.18 LLM 888.18 LLM	-7.67; 9.41; 0.75; 6.11; 3.82; 2.54; 4.07; -9.73; -0.02; 18.37
0	1	31.25 LLM 9.77 LLM 3.05 LLM 953.67 LLM 298.02 LLM 93.13 LLM 29.10 LLM 9.09 LLM 888.18 LLM 888.18 LLM 100.00 LLM	-7.67; 9.41; 0.75; 6.11; 3.82; 2.54; 4.07; -9.73; -0.02; 18.37
59-0043 59-0043	280.29	31.25 LLM 9.77 LLM 9.77 LLM 3.05 LLM 953.67 LLM 298.02 LLM 93.13 LLM 29.10 LLM 9.09 LLM 2.84 LLM 888.18 LLM 100.00 LLM 31.25 LLM 31.25 LLM	-7.67; 9.41; 0.75; 6.11; 3.82; 2.54; 4.07; -9.73; -0.02; 18.37; 20.66; 7.4;
59-0043 59-0043	280.29	31.25 LLM 9.77 LLM 9.77 LLM 3.05 LLM 953.67 LLM 298.02 LLM 93.13 LLM 29.10 LLM 9.09 LLM 2.84 LLM 888.18 LLM 100.00 LLM 31.25 LLM 9.77 LLM	-7.67: 9.41: 0.75: 6.11: 3.82: 2.54: 4.07: -9.73: -0.02: 18.37: 20.66: 7.4: -1.29-
0 H N N N N N N N N N N N N N N N N N N	280.29	31.25 LLM 9.77 LLM 9.77 LLM 3.05 LLM 953.67 LLM 298.02 LLM 93.13 LLM 29.10 LLM 9.09 LLM 2.84 LLM 688.18 LLM 100.00 LLM 31.25 LLM 9.77 LLM 3.05 LLM	-7.67; 9.41; 0.75; 6.11; 3.82; 2.54; 4.07; -9.73; -0.02; 18.37; 20.66; 7.4; -1.29; 1.21;
59-0043 59-0043	250.29	31.25 LLM 9.77 LLM 9.77 LLM 3.05 LLM 953.67 LLM 93.13 LLM 29.10 LLM 9.09 LLM 2.84 LLM 888.18 LLM 100.00 LLM 31.25 LLM 9.77 LLM 3.05 LLM 953.67 LLM	-7.67; 9.41; 0.75; 6.11; 3.82; 2.54; 4.07; -9.73; -0.02; 18.37; 20.66; 7.4; -1.29; -2.31; 1.54;
59-0043 59-0043	280.29	31.25 LLM 9.77 LLM 9.77 LLM 3.05 LLM 953.67 LLM 93.13 LLM 93.13 LLM 9.09 LLM 2.84 LLM 888.18 LLM 100.00 LLM 31.25 LLM 9.77 LLM 3.05 LLM 953.67 LLM 298.02 LLM	-7.67: 9.41: 0.75: 6.11: 3.82: 2.54: 4.07: -9.73: -0.02: 18.37: 20.66: 7.4: -1.29: 1.54: -0.79:
59-0043 59-0043	280.29	31.25 LLM 9.77 LLM 9.77 LLM 3.05 LLM 953.67 LLM 93.13 LLM 93.13 LLM 9.09 LLM 888.18 LLM 100.00 LLM 31.25 LLM 9.77 LLM 3.05 LLM 953.67 LLM 93.13 LLM	-7.67; 9.41; 0.75; 6.11; 3.82; 2.54; 4.07; -9.73; -0.02; 18.37; 20.66; 7.4; -1.29; -2.31; 1.54; -0.79; 1.52;
59-0043 59-0043	250.29	31.25 LLM 9.77 LLM 9.77 LLM 3.05 LLM 953.67 LLM 93.13 LLM 93.13 LLM 9.09 LLM 888.18 LLM 888.18 LLM 100.00 LLM 31.25 LLM 9.77 LLM 3.05 LLM 93.13 LLM	-7.67; 9.41; 0.75; 6.11; 3.82; 2.54; 4.07; -9.73; -0.02; 18.37; 20.66; 7.4; -1.29; -2.31; 1.54; -0.79; 1.52; 2.79;
59-0043	280.29	31.25 LUM 9.77 LUM 3.05 LUM 953.67 LUM 953.67 LUM 93.13 LUM 9.09 LUM 2.84 LUM 888.18 LUM 100.00 LUM 31.25 LUM 9.77 LUM 3.05 LUM 953.67 LUM 93.13 LUM 93.13 LUM 99.10 LUM 9	-7.67; 9.41; 0.75; 6.11; 3.82; 2.54; 4.07; -9.73; -0.02; 18.37; 20.66; 7.4; -1.29; -2.31; 1.54; -0.79; 1.52; 2.79; -0.27;
59-0043 59-0043	280.29	31.25 LLM 9.77 LLM 9.77 LLM 3.05 LLM 953.67 LLM 93.13 LLM 93.13 LLM 9.09 LLM 888.18 LLM 888.18 LLM 100.00 LLM 31.25 LLM 9.77 LLM 3.05 LLM 93.13 LLM	20.66\(7.4\) 20.66\(1.29\) -2.31\(1.52\) -7.67\(1.52\)

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59-0044		ì	i	
	341.211	<u> </u>		
59-0044		100.001uM	7.381	
<u> </u>		31.251uM	11.721	
	i	9.77 iuM	12.49	
	- 1	3.051uM	-0.521	
<u> </u>	4	953.67 inM	0.5	
	1	298.02 InM	6.111	
		93.131nM	-1.54:	
		29.101nM	19.141	
	1	9.09 InM	7.13;	
<u> </u>		2.84 nM	-2.061	
		888.181pM	5.84	
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59-0045	283.33			
59-0045 :	283.33	100.00 uM	52.37	64 460
		100.00 iuM 31.25 iuM	52.37 148.43	
59-0045 :	1.		JE.J.	192.960
59-0045	1.	31.25iuM	148.43	192.960 422.540
59-0045	† - 	31.25luM 9.77luM	148.43: 204.47: 280.3i	192.960 422.540 437.020
59-0045	† - 	31.25iuM 9.77iuM 3.05iuM	148.43: 204.47: 280.3i 254.82:	192.960 422.540 437.020 410.890
59-0045	1	31.25iuM 9.77iuM 3.05iuM 953.67inM 298.02inM	148.43: 204.47: 280.3i 254.82: 218.21	192.960 422.540 437.020 410.890 266.090
59-0045		31.25iuM 9.77iuM 3.05iuM 953.67inM 298.02inM 93.13inM	148.43: 204.47: 280.3i 254.82: 218.21 196.98!	192.960 422.540 437.020 410.890 268.090 183.730
59-0045	1	31.25iuM 9.77iuM 3.05iuM 953.67inM 298.02inM 93.13inM 29.10inM	148.43: 204.47: 280.3: 254.82: 218.21 196.98: 96.06:	192.960 422.540 437.020 410.890 266.090 183.730 80.440
59-0045	1	31.25iuM 9.77iuM 3.05iuM 953.67inM 298.02inM 93.13inM 29.10inM 9.09inM	148.43: 204.47: 280.3i 254.82: 218.21 196.98: 96.06: 67.35:	192.960 422.540 437.020 410.890 268.090 183.730 80.440 55.530
59-0045	1	31.25iuM 9.77iuM 3.05iuM 953.67inM 298.02inM 93.13inM 29.10inM	148.43: 204.47: 280.3: 254.82: 218.21 196.98: 96.06:	192.960 422.540 437.020 410.890 266.090 183.730 80.440
59-0045	1	31.25iuM 9.77iuM 3.05iuM 953.67inM 298.02inM 93.13inM 29.10inM 9.09inM	148.43: 204.47: 280.3i 254.82: 218.21 196.98: 96.06: 67.35:	192.960 422.540 437.020 410.890 268.090 183.730 80.440 55.530
59-0045	1	31.25iuM 9.77iuM 3.05iuM 953.67inM 298.02inM 93.13inM 29.10inM 9.09inM	148.43: 204.47: 280.3i 254.82: 218.21 196.98: 96.06: 67.35:	192.960 422.540 437.020 410.890 268.090 183.730 80.440 55.530
59-0045	1	31.25iuM 9.77iuM 3.05iuM 953.67inM 298.02inM 93.13inM 29.10inM 9.09inM	148.43: 204.47: 280.3i 254.82: 218.21 196.98: 96.06: 67.35:	192.960 422.540 437.020 410.890 268.090 183.730 80.440 55.530
59-0045	1	31.25iuM 9.77iuM 3.05iuM 953.67inM 298.02inM 93.13inM 29.10inM 9.09inM	148.43: 204.47: 280.3i 254.82: 218.21 196.98: 96.06: 67.35:	192.960 422.540 437.020 410.890 268.090 183.730 80.440 55.530
59-0045	1	31.25iuM 9.77iuM 3.05iuM 953.67inM 298.02inM 93.13inM 29.10inM 9.09inM	148.43: 204.47: 280.3i 254.82: 218.21 196.98: 96.06: 67.35:	192.960 422.540 437.020 410.890 268.090 183.730 80.440 55.530
59-0045 Ci	1	31.25iuM 9.77iuM 3.05iuM 953.67inM 298.02inM 93.13inM 29.10inM 9.09inM	148.43: 204.47: 280.3i 254.82: 218.21 196.98: 96.06: 67.35:	192.960 422.540 437.020 410.890 268.090 183.730 80.440 55.530
59-0045 CI 59-0046	1	31.25iuM 9.77iuM 3.05iuM 953.67inM 298.02inM 93.13inM 29.10inM 9.09inM	148.43: 204.47: 280.3i 254.82: 218.21 196.98: 96.06: 67.35:	192.960 422.540 437.020 410.890 268.090 183.730 80.440 55.530
59-0045 CI 59-0046		31.25iuM 9.77iuM 3.05iuM 953.67inM 298.02inM 93.13inM 29.10inM 9.09inM 2.84inM	148.43: 204.47: 280.3i 254.82: 218.21 196.98: 96.06: 67.35: 52.99i	192.960 422.540 437.020 410.890 268.090 183.730 80.440 55.530
59-0045 CI 59-0046		31.25iuM 9.77iuM 3.05iuM 953.67inM 298.02inM 93.13inM 29.10inM 9.09inM 2.84inM	148.43: 204.47: 280.3i 254.82: 218.21 196.98: 96.06: 67.35: 52.99i	192.960 422.540 437.020 410.890 268.090 183.730 80.440 55.530
59-0045 CI 59-0046	389.37	31.25iuM 9.77iuM 3.05iuM 953.67inM 298.02inM 93.13inM 29.10inM 9.09inM 2.84inM	148.43: 204.47: 280.3i 254.82: 218.21 196.98: 96.06: 67.35: 52.99i	192.960 422.540 437.020 410.890 268.090 183.730 80.440 55.530
59-0045 CI 59-0046	389.37	31.25iuM 9.77iuM 3.05iuM 953.67inM 298.02inM 93.13inM 29.10inM 9.09inM 2.84inM	148.43: 204.47: 280.3i 254.82: 218.21 196.98: 96.06: 67.35: 52.99: 79.33: 2.24: -1.67:	192.960 422.540 437.020 410.890 268.090 183.730 80.440 55.530
59-0045 Ci 59-0046	389.37	31.25iuM 9.77iuM 3.05iuM 953.67inM 298.02inM 93.13inM 29.10inM 9.09inM 2.84inM 100.00:uM 31.25iuM 9.77iuM 3.05iuM	148.43: 204.47: 280.3i 254.82: 218.21 196.98: 96.06: 67.35: 52.99i 79.33: 2.24: -1.67: -6.18i	192.960 422.540 437.020 410.890 268.090 183.730 80.440 55.530
59-0045 Ci 59-0046	389.37	31.25iuM 9.77iuM 3.05iuM 953.67inM 298.02inM 93.13inM 29.10inM 9.09inM 2.84inM 100.00:uM 31.25iuM 9.77iuM 3.05iuM 953.67inM	148.43: 204.47: 280.3i 254.82: 218.21 196.98: 96.06: 67.35: 52.99i 79.33: 2.24: -1.67: -6.18: 0.001	192.960 422.540 437.020 410.890 268.090 183.730 80.440 55.530
59-0046 59-0046	389.37	31.25iuM 9.77iuM 3.05iuM 953.67inM 298.02inM 93.13inM 29.10inM 9.09inM 2.84inM 100.00:uM 31.25iuM 9.77iuM 3.05iuM 953.67inM 298.02:nM	79.33: 2.24: -1.67: -3.63: 2.18.21: 196.98: 96.06: 67.35: 52.99: -79.33: 2.24: -1.67: -6.18: 0.001: -3.63:	192.960 422.540 437.020 410.890 268.090 183.730 80.440 55.530
59-0046 59-0046	389.37	31.25iuM 9.77iuM 3.05iuM 953.67inM 298.02inM 93.13inM 29.10inM 9.09inM 2.84inM 100.00:uM 31.25iuM 9.77iuM 3.05iuM 953.67inM 298.02:nM	79.33: 2.24: -1.67: -3.63: -3.63: -2.64: -1.67: -3.63: -1.64: -1.64: -1.64: -1.64: -1.64: -1.64: -1.64:	192.960 422.540 437.020 410.890 268.090 183.730 80.440 55.530
59-0045 Ci 59-0046	389.37	31.25iuM 9.77iuM 3.05iuM 953.67inM 298.02inM 93.13inM 29.10inM 9.09inM 2.84inM 100.00:uM 31.25iuM 9.77iuM 3.05iuM 953.67inM 298.02:nM 93.13inM 29.10inM	79.331 2.244 -1.671 -6.181 0.0011 -3.631 -6.421	192.960 422.540 437.020 410.890 268.090 183.730 80.440 55.530
59-0045 Ci 59-0046	389.37	31.25iuM 9.77iuM 3.05iuM 953.67inM 298.02inM 93.13inM 29.10inM 9.09inM 2.84inM 100.00:uM 31.25iuM 9.77iuM 3.05iuM 953.67inM 298.02:nM 93.13inM 29.10inM 9.91inM	79.33 224. 79.33 224. -1.67; -6.18; 0.001 -3.63 -0.84; -8.42; -3.92]	192.960 422.540 437.020 410.890 268.090 183.730 80.440 55.530
59-0045 Ci 59-0046	389.37	31.25iuM 9.77iuM 3.05iuM 953.67inM 298.02inM 93.13inM 29.10inM 9.09inM 2.84inM 100.00:uM 31.25iuM 9.77iuM 3.05iuM 953.67inM 298.02:nM 93.13inM 29.10inM	79.331 2.244 -1.671 -6.181 0.0011 -3.631 -6.421	192.960 422.540 437.020 410.890 268.090 183.730 80.440 55.530

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59-0047	303.37	i	
59-0047		100.001uM	-6.73i
		31.25luM	-0.731
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		953.67 InM	-10.11
		298.02 inM	
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		29.10InM	-7.281
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59-0048	384.50		ļ
59-0048		100.00 uM	-6.73
		31.25iuM	0.271
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		953.67 nM	-12.89
·		298.02 inM	
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		9.09InM	-0.021
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59-0049	251.29	į	
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	<u> </u>	31.25:uM	0:
		9 771uM	
		3.05 uM	4 77! 1.96¹
	i	953.67InM	8.691
1		298.02:nM	
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		29.10inM	1.69;
1		9.09:nM	1 -4 491
		2.84 inM	2.241
		885.18!pM	-0.31

59-0050	303.36	
59-0050	100.00 uM	45.79i
	31.25 luM	10.02)
	9.771uM	11.291
	3.051uM	-4.68:
	953.67 InM	-6.92:
	298.02 nM	-5.65
	93.13 nM	1.691
	29.10 nM	-7.57
	9.091nM	-12.051
	i 2.841nM	-13.631
	888.18 IpM	5.2
59-0051 59-0051	251.35	i
	100.001uM	32.36:
	31.25luM	-18.42i
	j 9.771uM	-0.551
	3.05!uM	-13.94
	953.67 nM	-12.02
	298.02 nM	-14.59i
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	29.10InM	-11.41
	9.09inM	-14 91
	2.84 InM	-10 74
	888.18 pM	-20.03

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59-0052	393.28		<u> </u>
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		31.25 uM	-13.32:
		9.771uM 3.051uM	-21.311
		953.67 inM	-11 08i -20.66:
		298.02 nM	-17.14
		93.13 nM	· -16.49i
		29.10(nM	-11.4:
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	!	2.84 nM	-11.081
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59-0053		1	;
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23-0023		100.00:uM 31.25:uM	-17 14
	!	9.77!uM	-21.31
		3.05 iuM	-9 47 -11.08:
	!	953.67 InM	-0.83;
	:	298.02 InM	-11 4)
		93.131nM	: -9 47'
!		29.10InM	-19.72;
	· · · · · · · · · · · · · · · · · · ·	9.091nM	-18.45;
	i	2.84 inM	-10.09!
<u> </u>		888.181pM	-2.76:

			
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59-0054	236.28		
59-0054	230.201	100.00 iuM	-20.04
	· · · · · · · · · · · · · · · · · · ·	31.251uM	-6.95
		9.77 LuM	8.31
:		3.051uM	-3.371
		953.67 InM	-2.41
:	i	298.021nM	-0.991
!		93.13 nM	i -0.99
	1	29.10inM	-1.941
		9.091nM	5.921
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59-0055	425.51		1
59-0055		100.001uM	-13.76:
		31.25 uM	-9.51
	<u> </u>	9.77 uM	-2.021
	<u> </u>	3.05 uM	3.241
		953.67 InM	-6.271
	· i	298.021nM	1 -4.051
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59-0056	512.34 [!]	-	
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		31.25/uM	4.87
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		3.05 uM	3.84:
	:	953.671nM	-5.07
	•	298.02!nM	i -7.29;
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59-0057	į	
59-0057	100.00 luM	
	31.25iuM	-24.150!
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	3.051uM	-5.980) -11.500
	953.67!nM	-13.000
	298.02 InM	-6.280
	93.131nM	-12.550
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	9.091nM	-8.5201
	2.841nM	-16.290
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59-0058	i	:
59-0058		1 4 670:
i	100.00 uM	4.170
	31.25luM 9.77luM	7.020;
	3.05luM	-1.790!
	953.67!nM	-7.320i -1.940i
	298.02 nM	-6.870:
	93.13 inM	-1.490:
	29.10inM	-8.3701
	9.09 nM	-5.0801
	2.84InM	-12 400:
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59-0059	÷	•
59-0059	100.00iuM	-18.770.
	31.25!uM	-16 1401
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	953.67:nM	6.010
:	i 298.02!nM	-1.9101
<u> </u>	93.131nM	-1.760
<u> </u>	29.10 nM	-9.100
	9.09InM	-8.220
	2 84 inM	-5.720!

31.25 tuM -1.520 9.77 tuM 1.030 3.05 tuM -1.180 953.67 tnM -1.3200 953.67 tnM -1.3200 953.67 tnM -3.570 129.10 tnM -7.340 9.09 tnM -1.310 9.09 tnM -1.310 9.77 tuM -17.770 9.77 tuM -17.770 9.30 tuM -1.4080 933.67 tnM -7.020 980.02 tnM -7.190 93.13 tnM -7.190 93.13 tnM -7.190 93.15 tnM -7.190				
59-0060 59-0060 100.00 iuM		,		- {
59-0060 59-0060 100.00 iuM				j
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59-0060 59-0060 100.00 iuM	's s	1		
59-0080 100.00 100.00 4.250 31.25 100.00 1.150 9.77 100.00 1.150 9.75 100.00 1.150 9.75 100.00 1.150 9.77 100.00 1.150 9.77 100.00 1.150 9.77 100.00 1.150 9.77 100.00 1.17 100 9.77 100.00 100 9.77 100.00 100 9.77 100.00	ОН	;		- [
59-0080 100.00 100.00 4.250 31.25 100.00 1.150 9.77 100.00 1.150 9.75 100.00 1.150 9.75 100.00 1.150 9.77 100.00 1.150 9.77 100.00 1.150 9.77 100.00 1.150 9.77 100.00 1.17 100 9.77 100.00 100 9.77 100.00 100 9.77 100.00	59-0060	İ		- 1
31,25 luM -14,520 9.77 luM 1,030 9.53,87 lmM -1,180 9.53,87 lmM -1,200 9.53,87 lmM -3,870 9.53,10 -3,870 9.53,10 -3,870 9.09 lmM -1,340 9.09 lmM -1,340 9.09 lmM -1,310 9.09 lmM -1,17,170 9.77 luM -17,170 9.30,5 luM -1,020 9.53,57 lmM -7,190 9.53,57 lmM -7,190 9.53,57 lmM -7,190 9.53,57 lmM -1,910 9.53,67 lmM -3,400 9.53,67 lmM -3,400 9.53,67 lmM -3,400 9.53,67 lmM -3,500 9.53,67 lmM -3,500 9.53,67 lmM -4,500 9.53,67 lmM -4,500 9.53,67 lmM -4,500 9.53,67 lmM -4,500 9.53,67 lmM -5,900 9.53,67 lmM -5,900 9.53,67 lmM -5,900 9.53,67 lmM -5,900	59-0060	! 100.00 uM	-4.2501	-
9.77 jul 1.030 1.030 1.180				
3.05 uM -1.180 953.87 nM -13.200 953.87 nM -1.3200 93.13 nM -3.870 93.13 nM -3.870 99.0 nM -1.310 99.0 nM -1.310 99.0 nM -1.310 99.0 nM -1.310 99.0 nM -1.310 99.0 nM -1.310 99.0 nM -1.700 99.0 nM -1.700 99.0 nM -1.700 99.0 nM -1.700 99.0 nM -1.700 99.0 nM -1.700 99.0 nM -1.910 99.0 nM -0.440				\neg
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93.13 M -3.670 29.10 M -7.340 9.06 M -1.310 2.84 M 0.290		298.02 nM		
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59-0061 100.00 iuM -17.8901 31.25 iuM -16.7701 9.77 iuM -17.1701 3.05 iuM -17.0201 953.67 inM -17.0201 298.02 inM -7.1901 93.13 inM -1.9101 9.09 inM -0.4401 9.09 inM -4.5601 2.84 inM -4.5601	но			
59-0061 100.00 iuM -17.8901 31.25 iuM -16.7701 9.77 iuM -17.1701 3.05 iuM -17.0201 953.67 inM -17.0201 298.02 inM -7.1901 93.13 inM -1.9101 9.09 inM -0.4401 9.09 inM -4.5601 2.84 inM -4.5601	59.0061			
31.25 tuM		1 200 00 444	1 17 6001	
3.05iuM -14.080 953.67inM -17.020 298.02inM -7.190 93.13inM -1.910 92.10inM -0.440 9.09inM -5.010 2.84inM -4.560 100.00iuM -13.940 9.70iuM -1.2.910 9.77iuM -4.560 9.75iuM -4.560 9.75iuM -4.560 9.75iuM -4.560 9.75iuM -4.560				
953.67 inM				
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\$9.3.13 \text{inM}				
29.10inM				
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2.84 inM -4 5601 S9-0062 59-0062 100.00 iuM -13.940 31.25 iuM -12.910 9.77 iuM -4.560 9.77 iuM -4.560 9.77 iuM -4.540 953.67 inM -5.900 298.02 inM -4.001 93.13 inM -1.6201				
59-0062 59-0062 100.00 uM -13.940 31.25 uM -12.910 9.77 uM -4.560 3.05 uM -4.540 953.67 nM -6.900 298.02 nM -4.100 93.13 nM -1.620				
59-0062 59-0062 100.00 uM -13.940 31.25 uM -12.910 9.77 uM -4.550 3.05 uM -4.540 953.67 inM -5.900 298.02 inM -4.100 93.13 inM -1.620		2.841nM	-4 56U1	
59-0062 59-0062 100.00 uM -13.940 31.25 uM -12.910 9.77 uM -4.550 3.05 uM -4.540 953.67 inM -5.900 298.02 inM -4.100 93.13 inM -1.620			•	
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59-0062 59-0062 100.00 uM			!	
59-0062 59-0062 100,00 uM -13,940 31,25 uM -12,910 9,77 uM -4,560 3,05 uM -4,540 953,67 nM -5,900 298,02 nM -1,620		j	!	
59-0062 : 100.00 iuM :-13.940 : 31.25 iuM :-12.910 : 37.25 iuM :-12.910 : 9.77 iuM :-4.560 : 3.05 iuM :-4.540 : 953.67 inM :-6.900 : 298.02 inM :-4.100 : 93.13 inM :-1.620				
59-0062 : 100.00 iuM :-13.940 : 31.25 iuM :-12.910 : 37.25 iuM :-12.910 : 9.77 iuM :-4.560 : 3.05 iuM :-4.540 : 953.67 inM :-6.900 : 298.02 inM :-4.100 : 93.13 inM :-1.620			i l	
59-0062 : 100.00 iuM :-13.940 : 31.25 iuM :-12.910 : 37.25 iuM :-12.910 : 9.77 iuM :-4.560 : 3.05 iuM :-4.540 : 953.67 inM :-6.900 : 298.02 inM :-4.100 : 93.13 inM :-1.620			j	
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31.25 uM			1	
31.25 uM -12.910	59-0062	i 100.001uM	-13.940	
9.77 uM -4.560	ı		-12.910	
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953.67inM				
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59-0063	100.00	
	100.001894	-2.5101
	31.25 uM	-6.1301
	9.77 uM	-8.9501
	. 3.0310M	-8.020
	953.67 inM	¹ -8.010I
	298.02 nM	-2.520i
	93.13InM	-5.810
	29.10 nM	-3.450:
	9.09 nM	l -4 .3901
	2.84 InM	-6.2801
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59-0064		
59-0064	100.00 uM	-23.0901
	31.25luM	-21.040
	9.77 uM	i 78.400i
	3.051uM	155.220
	953.67 nM	113.120:
	298.02 nM	30.640
	93.13 inM	
	29.10inM	15.240!
	9.09InM	22.150
	2.84inM	-0.770:
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9-0065		!
9-0065	i	
	100.00 tuM	-2.030
	31.251uM	-2.980
	9.771uM	-15.240:
	! 3.05luM	-15.4001
	953.671nM	-15.240
	298.02 nM	-10.520
	93.13InM	-13.830
i	29.10inM	-5.810
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:	2.84 inM	-7 070

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	10.0601
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1 9.77†uM	10.8501
3.05 uM	14.5101
953.67 InM	0.950i
298.02 nM	3.7801
93.13 nM	1.730
29.10 nM	-2.820
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100.00 uM	i -24.0401
31.25 uM	-24.8901
9.77 uM	-1.450
3.05 uM	60.9001
	133.6601
	75.330
	28.7601
	20.070!
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298.02 InM	17.300
298.02 InM 93.13 InM	17.300i 8.460i
298.02 inM 93.13 inM 29.10 inM	17.300 8.4601 -3.5301
298.02 InM 93.13 InM	17.300i 8.460i
	953.67 nM 298.02 nM 93.13 nM 29.10 nM 9.09 nM 2.84 nM

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59-0069		
70 0000	100.00 uM	5.490
	31.25lgM	9.6701
	9.77 uM	1 16.0901
	3.05 uM	-7.1801
	953.87 nM	-2.8401
	298.02 inM	-3.710
	93.13 nM	1 -11.180
	29.10 nM	-5.7901
	9.09 nM	-7.180!
	2.84 nM	4.7501
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59-0070		
59-0070	100.00 uM	-25.930
	31.25 uM	-23.000;
	9.77 uM	36.0601
	3.05 uM	214.2801
	953.67 nM	158.5301
	298.02 nM	72.8901
the second secon	93.13 nM	20.9401
	29.10 nM	7.7601
	9.09 nM	7.5901
	. 2.84 inM	-8.4001
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59-0071		
59-0071	100.001uM	: -18.650:
		-15.5401
		17.060
		176.090
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		31.260
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	29.10lnM	4.870
	9.09 nM	-7.3301
i i	2.84 nM	==4.660!

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59-0072		_!
59-0072	100.00!uM	-19.750:
	i 31.25 uM	-18.650!
	i 9.771uM	-16.430
	. 3.05 luM	-15.770
	953.67 inM	9.970
	298.021nM	74,740
	93.13InM	175.430
	29.10 nM	213.580
	9.09inM	164.320
	2.84 nM	
		119.1001
	888.18 pM	60.7701
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59-0073		1
59-0073	100.001uM	+3.010;
	31.25luM	4.8301
	9.77 uM	-9.660
	3.05 luM 953.67 lnM	4.6801
	298.021nM	-6.5001 -2.5101
	93.13InM	7.140
	29.10 nM	0.97
	9.091nM	-5.5:
	2.84InM	5.31
	1 :	. 3.31
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59-0074	·	
5-05.4	100 00 iiM	.2.85
59-0074	100.00 iuM 31.25 iuM	-2.85
3-00.4	31.25 uM	2.141
59-0074	31.25/uM 9.77/uM	2.141 -4.65i
59-0074	31.25 uM 9.77 uM 3.05 uM	2.141 : -4.65i i -3.51
59-0074	31.25 iuM 9.77 iuM 3.05 iuM 953.67 inM	2.141 -4.85i -3.51 -4.85
59-0074	31.25 iuM 9.77 iuM 3.05 iuM 953.67 inM 298.02 inM	2.141 -4.85i -3.51 -4.85i 9.95i
59-0074	31.25 iuM 9.77 iuM 3.05 iuM 953.67 inM 298.02 inM 93.13 inM	2.141 -4.85i -3.51 -4.85i 9.95i
59-0074	31.25 iuM 9.77 iuM 3.05 iuM 953.67 inM 298.02 inM 93.13 inM	2.141 -4.85i -3.51 -4.85i 9.95i

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59-0075	1	
59-0075		<u> </u>
	100.00\uM	-0.681
	V1.23,000	-10.161
	9.77 uM 3.05 uM	-5.35
	953.67 InM	-0.51
	298.02 InM	3.00
	93.13 nM	5.97 0.97
	29.10 nM	
	9.09 nM	-2.35 0.32
	2.84 inM	10.47
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59-0076		i
59-0076	100.001uM	10.121
	31.25 uM	-19.12:
	9.77 uM	9.29i
	3.05 uM	22.431
	953.67 InM	1 19.931
	298.02 nM	3.471
	93.13InM	19.93
	29.10 nM	10.631
	9.09 nM	14.281
	2.84 nM	11.31
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59-0077		
59-0077	1 100.00 uM	: 1
		-20.961
	31.25!uM 9.77!uM	-16.23!
	3.05 luM	-10.58!
	953.67 inM	-11.961
	298.02 nM	-19.441 -17.3
	93.13 nM	-13.79
	29.101nM	-15.62
	9.09 nM	1 -14.09
	2.84 inM	1 -14.41
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59-0078	!	
	100.00 iuM	-26.5401
	31.25 uM	-22.560!
· · · · · · · · · · · · · · · · · · ·	9.77 uM	71.530
	3.051uM	207.960
	953.67 nM	379.230
	298.02 nM	241,460
	93.13inM	136.100
	29.10inM	84.0201
	9.091nM	50.350
	2.84 inM	56.6001
	0.801nM	92.5201
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9-0079		
-0079	100.00 uM	-34 9801
	31.25iuM	
	9.77 uM	
	3.05 uM	
	953.67 InM	122.5801
	298.021nM	05.0101
	93.13(nM	04.000
	29.10InM	30.310
	9.09InM	33.490
	2.841nM	29.7601
		29.7601
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080	· 100.001uM	5.3901
	31.25luM	5.5601
i	9.77 uM	6 440:
	3.05 uM	: 2.440:
	953.67 InM	-5.0301
	298.02InM	7 660
	93.13tnM	-3.630!
	29.10InM	3.650;
<u> </u>	9.091nM	1.050
	. 2.84 inM	1 6.9401
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59-0081		_
1	200.00 tuM	82.8401
	1 31.25iuM 1 9.77luM	11.300: -8.670!
	3.051uM	: -8.6701 · 2 440;
	953.67 InM	-5.200
	298.021nM	-2.0801
	93.13InM	1.2201
	29.10InM	-2.250
	9.091nM	1.0501
	2.84 InM	-3.3001
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59-0082	<u> </u>	
59-0082 i	100.00 uM	111.79:
	31.25 uM	62.68
	9.77 luM	32.361
	3.051uM	! 9.11
	953.67 InM	-10.621
i	298.02 inM	l -1.86i
<u> </u>	93.13 nM	-6.891
	i 29.10InM	-3.911
	9.09 nM	2.221
<u> </u>	i 2.84 nM	16.36
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59-0083	<u> </u>	j
50,0000	1 100 00 iuM	10001
	100.001011	48.931
	31.25luM	40.91
	9.771uM 3.051uM	25.85
	: 953.67 InM	17.85
1	: 298.021nM	8.55i 3.9i
	93.13 inM	1 2.05i
	. 29.10inM	1 7.991
:	9.09inM	-3.911
	2.84 nM	3.351
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59-0084	;	
70.000	100.00: 14	<u> </u>
59-0084		37.670
	100.00 tuM	
	31.25 uM	26.0501

	953.67 InM	21.700.
	: 298.021nM	5.9001
	93.13inM	4.8701
	29.10inM	-10.9201
	9.091nM	: 10.080;
	2.84 nM	-2.080
		i
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59-0085		1
59-0085	100.00(uM	17.070
	31.25luM	41.890
	9.77 iuM	18.5001
	3.05iuM	20.3401
	953.67 InM	22.4901
	298.02 nM	8.090
	93.13 nM	11.790
	9.09 nM 2.84 nM	-0.7601 - 5.9401
	2.0-1114	5.9401
ОН		
59-0086	1	
59-0086	1 100.001uM	30.750
	i 31.25luM	31.190
	9.77 juM	<u>l</u> 14.790i
	1 3.05iuM	13.5001
	1 953.671nM	14.080
	298.021nM	3.940!
	. 33.131178	3.370
	29.10(nM 9.09(nM	-2.610i
	2.84InM	-5.040i 1 1.530I
59-0087		
59-0087	1 100.001uM	10.660
-	31.25luM	11.080
	i 9.771uM	3.100:
	3.05 uM	-1.320
	953.671nM	17.070
	: 298.021nM	7.950
	93.13!nM	4.4801
	1 29.101nM	4.5101
	9.091nM	0.470
;	2.841nM	9.6601

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59-0088		1
	100.00 uM	!
	31.25luM	
	9.77 uM	i i
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<u></u>	i 953.67 inM	
<u> </u>	298.02 nM	
	93.13InM	
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	9.09inM	
	2.84InM	1
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59-0089	[[
£0.0000		<u> </u>
	100.001uM	60.091
	31.25luM	116.251
	9.771uM	65.841
	3.05 uM	36.11
<u> </u>	953.67 nM	37.96
	298.021nM	18.42
	93.13 nM	6.331
	29.10InM	13.581
	9.09inM	0.75
	2.84inM	-5.771
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59-0090		
59-0090	100.00luM	<u> </u>
		1 32.771
	31.25tuM	24.631
	9.771uM	19.51
	3.05iuM	41.311
	1 953.67 InM	9.81
	298.02 nM	-1.76
	93.13 inM	3.53
	29.10InM	2.95
	9.09inM	2.95
	2.84InM	7.81
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59-0091	· i 1	
59-0091	100.001uM	0.26:
	31 281.14	7 0.40:
	31.25!uM	i 0.26! i 13.54

	9.77 (uM	95.94
	3.05iuM	87 71 -
	953.67InM	1 44 17:
	298.021nM	38.261
	93.13 InM	23.871
<u> </u>	29.101nM	21.65
i	9.09InM	10.951
·	2.84 inM	20.921
	1 1	į l
9-0092		
9-0092	100.001uM	-11.561
	31.25 uM	17,841
	9.77 uM	50.191
ı	3.05 uM	25.841
	953.67 inM	14.41
· · · · · · · · · · · · · · · · · · ·	298.02 nM	6.77
	93.13 nM	8.62i
	29.10InM	2.221
	9.09tnM	8.38
	2.84(nM	11
59-0093		
59-0093	100.00 uM	i -11.671
	31.251uM	15.021
	9.77 uM	35.441
	3.05 uM	29.89
	953.67 nM	1 22.881
····	298.021nM	19.561
<u> </u>	93.13(nM 29.10(nM	5.181 7.391
	; 29.101nM j 9.091nM	1 4.56
	2.84InM	5.9!
59-0094		
59-0094	100.001uM	-17.69:
	31.25luM	: 45.151
1	9.77 uM	24.971
	3.05 uM	19.811
	953.67!nM	9.35
	298.02 nM	1.36
		
	. 93.13InM	9.241
	i 29.101nM	0.481

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59-0095	1	
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33-0033	100.001uM	44.7
ļ	31.25 uM	47.61
	9.77 uM	12.78
	1 3.05 uM	21.49
	953.67 InM	15.01
	298.021nM	10.22
	93.13 nM	13.98
	29.10 nM	20.31
	3.02 IAN	10.9
	2.84 nM	9.21
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59-0096	!!!	
59-0096	100.00 uM	
	31.25luM	413.05
	i. 9.77luM	1 287.23
	3.05 uM	137.38
	1 953.67 nM	78.5
	298.02 inM	49.13
	00.404-44	50.68
	93.13 nM i	41.33
	9.09InM	20.20
	2.841nM	10.73
	2.0411W	22.17
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59-0097	1	}
59-0097	100.00 juM	77.47
	31.25 uM	77.97
	9.77 uM	160.93
	3.051uM	61.44
	1 953.671nM	47.78
	298.021nM	51.54
i	93.13InM	34.64
	29.10InM	43.18
	9.09!nM	= 39.91
	2.84 InM	99.91
	3.03.000	27 13

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59-0098	į į	·
59-0098 :	100.00 iuM	-1.38
	31.25 uM	186.89
	9.77 uM	! 221.7
<u> </u>	3.05 luM	164.69
<u>i</u>	953.67 nM	96.94
	298.02 InM	68.25
-	93.13(nM 29.10(nM	57
i	9.09inM	51.88
•	2.84 inM	41.29 33.43
() () () () () () () () () ()		33.43
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59-0099		
59-0099	100.00 uM	13.040;
	31.25luM	56.880!
<u> </u>	9.77 uM	119.3401
i	3.05 uM	237.420
	953.67 nM	285.4401
	298.02 nM	164.610
	93.13 nM	123.300
	29.10inM	69.2401
	9.09 nM	i 44.500l
	2.84InM	47.3901
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59.0100		
59-0100 I	400 001 14	10.000
33-0100	100.00 tuM	-10.0201 -10.7301
	31.25 uM 9.77 uM	-10.730: : 30.3401
	3.05luM	114.410
<u> </u>	953.67 inM	77.5401
	298.02 nM	40.290
!	93.13InM	35.7301
	29.10InM	: 28.290;
	9.09InM	17.480
	2.84 inM	11.470
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59-0101		
เรอาณา	100.001uM	25.370
	100.001uM	25.370

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	 	31.25:uM	12.440
		9.77 juM	-0.780
	<u> </u>	3.051uM	10.280:
		953.67 inM 298.02 inM	2.1101 7.8601
	!	93.13 nM	7.860) 1 1.140)
		29.10InM	2.8201
		9.09 nM	1 4.1501
		2.84 nM	5.590
S N N			
59-0102	394.34		
59-0102	284.34	100.001uM	
		31.25/uM	-24.3501
		9.77 uM	63.540
		3.05luM	1 121.320
		953.67 InM	79.5301
	<u>-</u> <u>-</u>	298.021nM	72.4601
	!	93.13 InM 29.10 InM	66.290) 45.690)
	<u>_</u>	9.091nM	45.690) 27.260)
		2.84 nM	42.3301
		888.18 pM	33.430
59-0103	313.38		
	313.361	100.00 uM	20.00
		31.25 uM	-29.69
		9.77 uM	-29.53i -28.22!
		3.05 UM	-20.22
		953.67InM	-5.581
	i	298.02 nM	54.151
	i	93.13 nM	170.951
	i	29.10inM	222.87
	1	9.09inM	210.391
	!	2.84 inM	203.41
		0.80inM	114 551
59-0104	297.31		
		100.00 uM	-29.84
		31.25]uM	-26.72
		9.77 luM	-29.21
		3.05 uM	27.05
		953.67 InM	24.37
		298.02 nM	196.42
	1	93.13 inM	213.69

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		29.10(nM=F # "		
		9.091nM	245.421	
	<u></u> -	2.84 inM	182.45:	_
		0.80InM	119.55	
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59-0105	267.29			İ
		100.001uM	-25.72	_
	i	31.25 luM	-15.89	
		9.77 uM	31.7	
		3.05 uM	54.17	_
	1	953.67 nM	53.67	
		298.02 nM	41.35	
		93.13 nM	44.5	
		29.10 nM	39.02	
	I	9.09 nM	25.38	
	<u>i</u>	2.84 nM	31.71	
		0.80 inM	18.05i	
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59-0106	297.31			1
		100.00 uM	-14.05	
		31.25 uM	223.52	
		9.77 uM	202.581	
		3.05 uM	107.73	
		953.67 InM	71.3	
		298.021nM	44.84	
		93.13InM	26.541	
!	<u> </u>	29.10 nM	23.05	
		9.091nM	27.871	
		2.84 nM	12.23	
	<u> </u>	0.80InM	11,41	
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59-0107	332.38			
		100.00 uM	48.55	
		31.25ĺuM	22.87	
	<u></u>	9.77 uM	7.19	
	<u> </u>	3.05 luM	0.65	
	<u>i</u>	953.67 InM		
		298.02 nM	-3.92	
		93.13 nM	1.09	_
<u> </u>		29.10 nM	-15.69	

		9.09 mMG/ 8***	: 4 = 11 32 2 = 3.5
	1	2.84 nM	-2.621
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59-0108	316.31		
	3.0.5.1	100.00 uM	1 222 22
		31.25 uM	227.73
		9.77 uM	96.02
		3.05 uM	58.57
		953.67 nM	37.23
		298.02 nM	18.94
		93.13 nM	25.68
		29.10 nM	-4.8 2.62
1		9.09 nM	
		2.84 nM	-4.8
		0.80 nM	3.321
		0.001nM	4.14
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59-0109	316.31		1 1
	310.311	100.00 uM	49.491
	1	31.25 uM	43.121 27.641
		9.77 uM	
		3.05 uM	5.89
		953.67 nM	
		298.02 InM	13.51! 7.85!
	<u> </u>	93.13 nM	
			3.71
		29.10 nM	-3.27
,	<u>-</u> <u>:</u>	9.09 nM 2.84 nM	5.01
		0.80 nM	4.581
		U.BUIRM	6.98!
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59-0110	285.29	1	
	<u> </u>	100 00	4
	 -	100.00 uM	65.11
		31.25 uM	67.05
	!-	9.77 uM	35.27
		3.05 uM	25.26
		953.67 nM	27.011
		298.02 nM	15.24

	1	93.13 InMC/ 5	10.68
			1 5.891
		29.10 nM 9.09 nM	5.69:
			10.241
		2.84 inM	4 14
		0.80 nM	4 141
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59-0111	152.15		
		100.00 iuM	23.360
		31.25 uM	22.3301
		9.77 uM 3.05 uM	12.250
		953.67 InM	2.190
	i	298.02 inM	1.2301
		93.13 nM	2.430
		29.10 nM	6.350
		9.09 nM	4.350
		2.84 inM	4.3501
		0.80 nM	3.230
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59-0112	149.19		
1	198.181	100.00IuM	1 2.670
		31.25 uM	4.670
	İ	9.77 uM	2.750
		3.051uM	3.790
		953.67InM	4.2701
	<u> </u>	298.02 nM	1.150
·		93.13inM	9.6301
<u> </u>		29.10InM 9.09InM	0.9201
		2.84InM	12.9001
	1	0.80InM	2.990
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59-0113	274.37		
<u> </u>		100.00!uM	22.010
 	!	31.25 uM	25.940
		9.77 uM 3.05 uM	7.500i 3.070l
		953.67 InM	-0.760
-		298.021nM	-4.690
		93.13inM	4.790
		29.10InM	5.090
		9.09 nM	: 0.150
		2.84 inM	-0.250
	ī	0.80InM	0 1501

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5 9 -0114	1		1 1
39-0114	475.54		!
		100.001uM	52.030;
	! -	31.25 uM	36.120!
		9.77 uM	25.8401
		3.05 luM	16.6701
		953.671nM	12.5401
	 	298.02 inM	9.4201
	 	93.13 nM 29.10 nM	-1.0601
		9.09InM	2.1601
	 	2.84 inM	-5.000)
		0.80 nM	2.4701
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59-0115		1.	
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		100.00 uM	· 73.700i
	 	31.25 uM	2.770
	 	9.77 uM	-10.430
	<u> </u>	3.05 uM	-12.340
	 	953.67 InM	-13.7501
	 	298.02 nM	-13.960)
	 	93.13 nM	-11.940
		29.10 nM	-9.8301
		9.09†nM 2.84†nM	-8.8201
		0.80 nM	-0.950
		U.BUIRM	-0.0501
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9-0116	269.30		
	105.50	100 00 1144	31 380
		31.25luM	
	·	9.77 uM	
		3.05 uM	231.0701
		953.67 InM	240.670; 132.020;
		298.021nM	75.820
		93.13 nM	53.250
		29.10InM	47.5001
		9.09InM	39.440
		2.84 nM	42.170
		0.80 nM	31.180
			31.100
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9-0117	268.38		
	•	100.001uM	-68.520

		24.25	
		31.25 luM	237.450 pr / 3
		9.77 UM	1 111.6301
		3.05 uM 953.67 nM	64.340
			4.740
		298.021nM 93.13inM	-19.2701
	 -	29.10InM	-26.6601
		9.09 nM	-28.880
			-42.180
		2.84 nM 0.80 nM	-41.300)
	· · ·	U.80 NM	-39.2201
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59-0118	313.36		
		100.00 uM	-67.170
		31.25 uM	-56.580)
		9.77 uM	-58.060
		3.05 uM	-55.7201
		953.67 InM	-48.2001
		298.021nM	-50.300!
		93.13 nM	-33.310
		29.10inM	-47.340
		9.09inM	-49.310
		2.84 nM	-56.2001
		0.80 nM	-57.310
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59-0119	~ 314.34		-
		100.00 uM	167.5001
		31.25 uM	-29.240
		9.77 uM	-57.800)
		3.05 iuM	-52.0301
		953.67 nM	-54.2401
		298.02 inM	-53.8701
		93.13 nM	-38.110
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	504.49	93.13 nM 29.10 nM 9.09 nM 2.84 nM 0.80 nM	-38.110 -55.100 -52.270 -53.500 -43.650
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	504.49	93.13 nM 29.10 nM 9.09 nM 2.84 nM 0.80 nM	-38.110 -55.100 -52.270 -53.500 -43.650 -43.650 -82.790 -80.470 -66.800
59-0120	504.49	93.13 nM 29.10 nM 9.09 nM 2.84 nM 0.80 nM	-38.110 -55.100 -52.270 -53.500 -43.650 -82.790 -80.470 -66.800 -80.790
59-0120	504.49	93.13(nM 29.10(nM 9.09(nM 2.84(nM 0.80(nM 100.00(uM 31.25(uM 9.77(uM 3.05(uM 953.67(nM	-38.110 -55.100 -52.270 -53.500 -43.650 -43.650 -82.790 -80.470 -66.800 -80.790 -54.240
59-0120	504.49	93.13 nM 29.10 nM 9.09 nM 2.84 nM 0.80 nM	-38.110 -55.100 -52.270 -53.500 -43.650 -82.790 -80.470 -66.800 -80.790

:		29.10inM	.60.200
	- :	9.09inM	
			50.300
		2.84 inM	-50.3001
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59-0121	245.29	1	
	Ī	100.00 uM	-79.690
		31.25 uM	i -75.590)
		9.77 uM	25.8501
		3.05 uM	94.8501
		953.67 nM	43.910
		298.02 inM	
	i	93.13 inM	-1.800
		29.10 nM	4.150
		9.09 nM	-22.050
		2.84 nM	-31.110
<u> </u>		0.80InM	-26.760
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59-0122	333.39		
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		100.001uM	-19.0501
		31.25 uM	-12.080
	!-	9.77 uM	-7.6101
		3.05 uM	1 25.2101
		953.67 InM	83.5801
		298.021nM	87.2201
	<u></u>	93.13InM	63.8901
————— <u>———</u>		29.10InM	1 42.6801
		9.091nM	45.3201
	i	2.84 inM	37.7801
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59-0123	347.42	l	1
		100.001uM	34.4301
		31.25luM	34.710
		9.77 uM	38.6201
	<u>i</u>	3.05 uM	55.100
		953.67 inM	51.900
		298.021nM	41.410
	———— <u>i</u> —	93.13 nM	
			29.970
		29.10 nM	13.760
		9.09inM	17.1201
	 _	2.84 nM 0.80 nM	1 13.4801
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59-0124	350.44	ļ	
1	i	100.00 uM	56.640i
		31.25 uM	61.500!
		9.77 uM	145.8801
		3.05 luM	135.830!
		953.67 InM	268.990
<u> </u>		298.02 inM	224.2901
		93.13 nM	134.6501
		29.10 nM	91.690
<u> </u>		9.09inM	60.390
		2.64 inM	63.0601
		0.80inM	51.460
59-0125	372.45		
i i		100.00 uM	-6.7801
		31.25 uM	67.530
•		9.77 iuM	54.1201
		3.051uM	28.700
1		953.67 InM	21.580
		298.021nM	22.280
i	1	93.13InM	22.700
<u> </u>	· · · · · ·	29.10inM	1.6301
	<u> </u>	9.09inM	15.7001
	!	2.84 nM	9.8401
		0.801nM	8 4601

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59-0126	260.30		1	j
	<u> </u>	100.001uM	-17.390)	 -
	<u> </u>	31.25 luM	-13.100	
	!	9.77 uM	9.270	
	<u> </u>	3.05 uM	40.530	
	<u> </u>	953.67 nM	21.390	
		298.02 inM 93.13 inM	25.660	
		29.10InM	9.430	
		9.09 nM	6.360) 6.510	
		2.84InM	0.0801	
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9-0127				
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		31.25 uM	-21.820	<u> </u>
		9.77 uM 3.05 uM	-6.060	
		953.671nM	-3.9001	
		298.02 inM	-8.820i -6.200i	:
		93.13InM	11.880	
		29.10inM	1.610	
<u> </u>		9.09InM	3.600i	
		2.84 InM	-2.070	;
	i	0.80 nM	4.2201	
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	436.34			!
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		31.25luM		1
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		3.051uM 953.671nM		
		298.021nM	1	
		93.13/nM	:	
		• €9.10 nM		<u> </u>

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59-0129	277.71			ŀ	1	
		100.00	luM	-20.4	61	-
		31.25	иM	-21.2	11	
	l l	9.77		44.3		
<u> </u>		3.05		4.3	81	
		953.67			9	
	1	298.02			61	i
		93.13		2.0		1
	<u> </u>	29.10 9.09		4.2		1
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		953.67 InM	-13.541	
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59-0133		31.251uM 9.771uM 3.051uM	-16.91 i -17.31 i -16.71	i
59-0133	i	31.251uM 9.771uM 3.051uM 953.671nM	i -16.91i i -17.31i : -16.7i i -9.34i	
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59-0133		31.251uM 9.771uM 3.051uM 953.671nM 298.021nM 93.131nM	i -16.91 i -17.31 i -18.7i i -9.34i i -12.69 i -11.23	
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59-0133		31.251uM 9.771uM 3.051uM 953.671nM 298.021nM 93.131nM 29.101nM 9.091nM	i -16.91 i -17.31 i -16.7i i -9.34i i -12.69 i -11.23 i -17.74 i 6.02	
59-0133		31.251uM 9.771uM 3.051uM 953.671nM 298.021nM 93.131nM 29.101nM	i -16.91 i -17.31 i -16.7i i -9.34i i -12.69 i -11.23 i -17.74	

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59-0135	356.39		•	. !	1
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59-0138 340.81	}		į
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	93.13inM	2.261	
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	3.051uM	30.421	
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59-0140 289.17			<u> </u>
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59-0141 437.33			
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	93.13inM	24.361	1
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59-0142 379.21	93.13 inM 29.10 inM 9.09 inM 2.84 inM 0.80 inM	24.36 1 18.6 1 26.7 1 15.96 1 7.87	
59-0142 379.21	93.13inM 29.10inM 9.09inM 2.84inM 0.80inM	24.36 1 18.6 1 26.7 1 15.98 1 7.87	
59-0142 379.2	93.13inM 29.10inM 9.09inM 2.84inM 0.80inM	24.36 18.6 26.7 15.98 7.87 9.43 33.72	
59-0142 379.2	93.13inM 29.10inM 9.09inM 2.84inM 0.80inM 100.00iuM 31.25iuM - 9.77iuM	24.36 18.6 26.7 15.98 7.87 9.43 33.72 47.33	
59-0142 379.2	93.13inM 29.10inM 9.09inM 2.84inM 0.80inM 100.00iuM 31.25iuM 9.77iuM 3.05iuM	9.43 9.43 33.72 47.33	
59-0142 379.2	93.13inM 29.10inM 9.09inM 2.84inM 0.80inM 100.00iuM 31.25iuM - 9.77iuM	24.36 18.6 26.7 15.98 7.87 9.43 33.72 47.33	

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59-0143	447.29	ĺ		i
		100.00 uM		
		31.25 uM	0.41	<u> </u>
	 	9.77 uM	34.391	<u> </u>
		3.05 uM	42.211	
		953.67InM	50.57	1
		298.02 InM	36.94	i
	1	93.13 nM	27.231	
		29.10 nM	16.991	
			19.27:	
		9.09 nM	14.421	
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		0.80 nM	23.72	
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59-0144	316.40	}		Į.
i·		100.001uM	-14.591	!
		31.25 uM	-4 441	
		9.77 uM		
		3.05 luM	47.11	
		953.87 InM	53.891	<u> </u>
		298.02 nM	43.11	
		93.13InM	29.21	
			18.51	· · · · · · · · · · · · · · · · · · ·
		29.10InM	12.91	•
		9.09 inM	5.541	
	<u>-</u> !	2.84 (nM	3.71	i
	:	0.80InM	5.87	
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9-0145		İ		
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		100.00 uM	435.91	
	i	31.25 uM	422.15	· · · · · · · · · · · · · · · · · · ·
		0.33	446.93	1
		9.77 iuM	, 4-0.831	•
		3.05 uM	434.17	
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	:	3.05 uM 953.67(nM	434.17 	
		3.05 uM 953.67 (nM 298.02 nM	238.34L	

		2.84 InM	5.271	
		0.801nM	3.55	
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59-0146	246.27			
		100.00 luM	-63.05	
		31.25 uM	4 421	
		9.77 luM	-13.73	1
	 	3.051uM	-16.45	
1		953.671nM	-35.47	
		298.02 InM	-51.25 -50.13	<u> </u>
		93.13 inM 29.10 inM	-42.92	
		9.09 nM	-45.641	
	_	2.84 inM	-56.58	-
		0.80InM	-39.68	-
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59-0147	314.36			
		100.00 luM	-85	
		31.25 uM	-851	
		9.77 uM	-80.291 -41.671	
		3.051uM 953.671nM	78.691	
	· <u>. </u>	298.02 InM	269.131	
		93.13 nM	323.59	<u> </u>
		29.10InM	339.681	i
	i i	9.09 nM	270.481	
	i i	2.84 InM	245.58	
		0. 80 inM	180.331	
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59-0148	291.35		<u> </u>	
	 	100.001uM	-68.38	
	 	31.25 uM	-36.331	
	\	9.771uM	-2.31 12.121	<u> </u>
	+	3.05 luM 953.67 lnM	-2.42	
	 	298.02 nM	-16.21	- i
	i 	93.13InM	-30.87	<u> </u>
	† 	29.10InM	-35.581	
···	† 	9.09 inM	-39.07	
	T	2.84InM	⊸1.18 T -	
	: :	0.80 nM	-45.531	

				
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59-0149	329.33			
	1	100.00 LuM	-16.9	
		31.25 JuM	-1.8	
		9.77 uM	-0.53	
	: 1	3.05 LuM	15.29	
	!	953.67 nM	78.78	
	<u> </u>	298.02 nM	163.5	<u> </u>
	!	93.13 inM	223.57	
		29.10 nM	173.93	
		9.09 nM	122.31	
		2.84 inM	98.021	1
	<u> </u>	0.801nM	69.06	
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59-0150	304.00	1		
	304.39	100.00 luM		
		31.25 uM	63.32	!
		9.77 uM	193.53	i
		3.05 uM	419.26	
		953.671nM	497.211	<u> </u>
		298.021nM	295.191 1 193.351	
		93.13InM	99.461	1
		29.10 nM	69.961	
		9.09InM	59	
	ī	2.84 nM	52.16	
		0.80inM	48.751	
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J-0151	278.311			
-0151		100.00 uM	-6.6601	
		31.251uM	16.2401	
		9.771uM	18.300	
		3.051uM	11.690!	
		953.67 nM	8.500	
		298.02 inM	9.070	i
		93.13 nM	6.110	
		29.10 nM	5.880	
	!	9.09 nM	! 7.700	1
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		0.80InM	1.210	

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59-0152	266.275		ļ			
59-0152		100.001u	M	-6.890		
		31.25 u		12.490		
		9.77 u	M i	21.950		
		3.05 u	M	12.820		
		953.67 In	M	7.350		
	_	298.02 n	M	4.290		
	1	93.13 in	M I	9.750		
		29.10 n	M	4.860		
i		9.09 n		1.320	· · · · · · · · · · · · · · · · · · ·	
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59-0153	282.73			ļ	Į.	
59-0153		100.00 u	M	-4.150		
i		31.25 lui	М	-0.390	<u> </u>	
		9.77 ul	M	11.120	·	
		3.05 u	M	14.540	1	
		953.67 In	M	9.520		
A 100 A 100		298.02 n	M -	11.570		L
		93.13 ni	M	-0.160		
		29.10 n	M . 1	1.550		
		9.09 n	M ·	-0.960		
		2.84 n		4.730		
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59-0154	262.312					
	262.312	100.00 lu	M	0.290		
59-0154		31.25 u	M	24.570		
59-0154		31.25 u 9.77 u	M M	24.570 15.680		
59-0154		31.25 u 9.77 u 3.05 u	M ! M ! M ;	24.570 15.680 14.540		
59-0154		31.25 u 9.77 u 3.05 u 953.67 n	M	24.570 15.680 14.540 13.170		
59-0154		31.25 u 9.77 u 3.05 u 953.67 n 296.02 n	M I	24.570 15.680 14.540		
59-0154		31.25 ul 9.77 ul 3.05 ul 953.67 nl 298.02 nl 93.13 nl	M I	24.570 15.680 14.540 13.170		
59-0154		31.25 u 9.77 u 3.05 u 953.67 n 296.02 n	M I	24.670 15.680 14.540 13.170 5.540		
59-0154 59-0154		31.25 ul 9.77 ul 3.05 ul 953.67 nl 298.02 nl 93.13 nl	M I M I M I M I M I M I M I M I M I M I	24.670 15.680 14.540 13.170 5.540 2.690		
59-0154 59-0154		31.25 u 9.77 u 3.05 u 953.67 in 298.02 in 93.13 in	M I	24.670 15.680 14.540 13.170 5.540 2.690		

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3.05 LMM -0.220 93.57 LMM -0.890 298.02 LMM 5.990 92.13 LMM -2.250 9.09 LMM -1.900 9.09 LMM -1.900 9.09 LMM -1.130 9.77 LMM -2.890 9.77 LMM -2.890 9.77 LMM -3.890 9.78 LMM -3.890 9.78 LMM -3.890 9.79 LMM -3.890 9.79 LMM -3.890 9.79 LMM -3.890 9.70 LMM -3.890 9		!	9.77 LuM		
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59-0156 333.391 100.001uM 5.8401 31.251uM 2.0501 9.771uM 7.0601 3.051uM 6.8901 928.021mM -1.8801 93.131mM -3.5501 29.001mM -7.3401 9.091mM -7.3401 2.841mM 2.8501 0.801mM 2.8501 0.801mM 2.5001 100.001uM 5.8402 100.001uM 5.8403 100.0		<u> </u>	0.80inM		
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100.001uM 5.8401	·	333.391			
31.25 tuM 2.0501 9.77 tuM 7.960	59-0156		100.00JuM	5.8401	
3.05 uM 6.890 953.67 nM -0.370 1.860 953.67 nM -3.550 93.13 nM -3.550 9.99 nM -1.590 1.860 9.99 nM -1.590 1.860 1.8		!i	31.25 uM		
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92-6007	36.323
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92-8215	105 122 114
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92-8258	162,102	uМ
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308.447	16.210	
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92-8362		
92-8362	154.647	
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323.318	30.929 15.465	
323.316		
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92-8372		
92-8372	150.045	Mu
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92-9183		

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850-7449	69.936	М
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850-8613	151.319	шМ
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850-8637	85.518	Mu
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895-0857	159.028	цМ
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896-0984	162.695	uM.
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895-3306	172.170	иМ
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	16.243	
307 821	16.243 3.249	
	16.243	

-21.41 13.40 114.46 52.12 38.29
6.97 283.99 447.51 304.86 100.46
-17.18 24.54 100.12 60.37 27.85
 -6.47 213.42 107.83 48.75 18.27

895-5960		
895-5960	103.348	
	10.335	
483 798	2.067	
	0 413	<u> </u>
	0.083	
S NH S S S S S S S S S S S S S S S S S S		
895-6363	467.555	
035-033	167.555	UM
	16,755	
298.408	3.351	
	0.670	
	0.134	
995-6643		
895-6643	145,862	ωM
	14.586	
342.786	2.917	
	0.583	
	0.117	
0° 0° S 895-7828		
896-7828	184.973	LIMA
	18.497	<del></del>
270.31	3.699	-
, 270.31	J. (25/2)	i
	0.740	$\neg$
	0.740 0.148	

-10.03 155.04 62.07 34.47 7.24
-10.45 21.59 101.77 54.91 24.15
100.09 74.25 16.86 -0.89 -7.94
32.44 -29.24 85.15 125.64 -30.80

NH ₂		
896-7986	222.00	<del>  _</del>
	223.936	_
222.27	22.394 9 4.479	
223.27		
	0.898	_
	0.179	<del> </del>
995-7997		
896-7997	ļ	
0357337	176.461	υM
	17.646	
283.34		Ш
	0.706	
	0.141	
Br NH		
895-8053	134.398	uM
	13.440	
372.03	2.686	
	0.538	
	0.108	
HO OH NH OH OH		
895-8137	169.326	M

122.070 3.900 -7.790 5.520
-2.270

		<del></del>
	16.933	
295.28	3.367	<u>'</u>
	0.677	
	0.135	_
	1	+-
895-8185	1	
895-8185	219.057	uM
	21.906	<u> </u>
228.251		-
28.21		<del></del>
	0.876	<u> </u>
	0.175	L
855-8286		
895-8286	142.765	Mu
	14.277	
350.225	2.855	$\neg$
	0.571	-
	0.114	
0 LZ Z Z Z Z Z Z Z Z Z Z Z Z Z Z Z Z Z Z		
895-8383	191.774	
	19.177	<del></del>
260.724		$\dashv$
202724	3.835	
	0.787	$\dashv$
	0.153	

142.210 40.390 17.850 -10.890 6.580
-44.020 76.460 135.940 77.030 37.630

895-6962 895-6962	165.876	
	16.588	
301.43	3.318	
	0.664	
	0.133	
	-	$\vdash$
895-9683 895-9683	112555	
030-6083	113.552	<u>w</u>
	11.355	
440.326	2.271	
	0.454	
	0.091	_
N N N N N N N N N N N N N N N N N N N		
895-9898	178.349	-
	17.835	
	3.567	_
	0.713	- 1
1	0.143	

54.72 159.21 113.97
41.96 38.28
-20.67
12.55 0.62 -0.69
-29.16
 0.62 182.84 118.55
42.75

	<del>,</del>	
N N N N N N N N N N N N N N N N N N N		
896-0122	190.610	uM.
	19.061	
262.316		
	0.762	
	0.152	
S CI		
896-0246	45 4 200	
896-0246	154.888	шм
	15.489	
322.814	3.098	
	0.620	
	0.124	—
896-0255		
896-0255	123.000	
	12.300	
408.504	2.460	-+
	0.492	
	0.098	$\dashv$
896-03-45		
	107.532 10.753	u <b>M</b>

BNSD001D: <WO 981726741 1 >

. 464.979	2.151	
	0.430	
	0.086	
ZZ O		
896-0390		
896-0390	128.718	uM
	12.872	
388.445	2.574	
	0.515	
	0.103	Щ
896-0536		
896-0535	132.810	шМ
	13.251	
376.478	2.656	
	0.531	$\dashv$
	0.106	-
205.0554 806.0554		
896-0554	121.499	uM
	12.150	
411.527	2.430	
	0.486	
	0.097	

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105.46	;
115.43	•
-16.33 105.45 115.43 53.86 27.03	,
27.00	:

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OHN		
896-0686		
896-0686	191.774	uМ
	19.177	
260.724	3.835	
	0.767	
	0.153	
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896-0892		
896-0692	131.269	uM
	13.127	
390.897	2.625	
	0.525 0.105	
	0.105	
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896-0719 896-0719	C4 C55	444
W-0-113	91.950 9.1 <b>9</b> 5	4
543.774	1.839	
5.5.774	0.368	-
	0.074	
CI CI		
N CI		
896-0773		
896-0773	147.228	W
	14.723	
339.609	2.945	
	0.589 0.116	

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-19	9.80
176	6.04
115	0.02
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	5.49 7.43 7.43
	5.49 7.43 7.43 0.04
	5.49 7.43 7.43 0.04 5.16
	5.49 7.43 7.43 0.04 5.16
	5.49 7.43 7.43 5.04 5.16
	5.49 7.43 7.43 5.04 5.16
12 5 3	5.49 7.43 7.43 0.04 5.16
12 5 3	5.49 7.43 7.43 5.04 5.16
12 5 3	5.49 7.43 7.43 5.04 5.16
12 5 3	5.49 7.43 7.43 5.16
12 5 3	5.49 7.43 7.43 5.04 5.16
12 5 3	5.49 7.43 7.43 0.04 5.16
12 5 3	5.49 7.43 7.43 5.16
12 5 3	5.49 7.43 7.43 5.04 5.16
12 9 3	
12 5 3	5.49 7.43 7.43 5.04 5.16
12 5 3	
12 9 3	
12 5 3	
12 9 3 3 -1 17 22	
-1: 17: 22: 5: 5: 10: 17: 22: 5:	

NH S NH		
896-0819 896-0819		
890-0819	124.219	
	12.422	
402.51		
	0.497	_
	0.099	
NH 0 N=0		
896-0853	157.546	UM.
	15.755	;
317.367		
	0.630	
	0.126	
NH 0 S N N		
896-0921	4745	
	174.583	IM
286.397	17.458	
250.397	3.492	$\dashv$
	0.696	$\dashv$
	0.140	

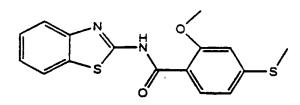
	İ
1	
-16.20 70.00	
165.79	
82.61	
49.06	<u> </u>
	]
	]
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-27.08	
75.38 208.69	
33.08	
32.63	
-19.59	
44.07	
103.23	
54.02 23.86	

NH NH O	
896-0936	
896-0936	184.314 uM
	18.431
271.276	
	0.737
<del></del>	0.147
896-CR559	
896-0959	103.798 uM
	10.380
481.703	
	0.415
	0.083
898-1201	
896-1201	108.343 uM
	108.343 uM 10.834
	10.534
896-1201	10.534

-16.20 153.61 184.53 79.16 32.61
-1.73 102.48 61.61 63.56 48.27
-45.70 92.57 191.83 47.22 58.25

896-1301		
896-1301	97.922	UM
	9.792	
510.612		
	0.392	-
	0.078	
5 5 898-1349		
896-1349	115.883	Mu
	11.588	
431.47	2.318	
	0.464	
	0.093	
NH NH NH		
896-1362		
896-1362	142.749	uM
<u> </u>	14.275	
350.268	2.855	
	0.571	
1	0.114	コ

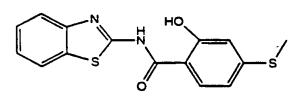
-24.32 102.49 139.28 97.89 23.45
-39.92 55.08 122.68 67.25 3.39
1.073.91 1.062.17 884.71 -9.82 -20.37



59-0072

S S S

59-0070



59-0144

59-0147

FIG. 5A

The first of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the cont

Max: 215 % EC50: < 0.8 nM

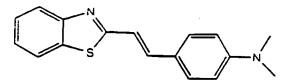
Max: 121 % EC50: 30 nM

Max: 214 % EC50: 200 nM

Max: 54 % EC50: 2 μM

Max: 340 % EC50: < 0.8 nM

.



Max: 285 % EC50: 3 nM

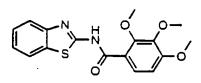
59-0099

Max: 269 % EC50: < 0.8 nM

Max: 200 % EC50: 30 nM

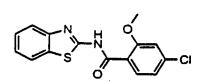
59-0210

FIG. 5E



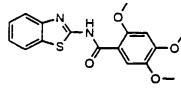
59-0192

Max: 155 % EC50: 20 nM



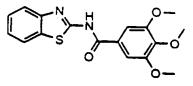
59-0195

Max: 155 % EC50: 20 nM

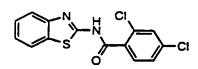


59-0193

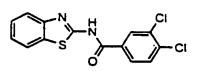
Max: 95 % EC50: 30 nM



59-0194 Inactive

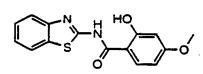


59-0196 Inactive



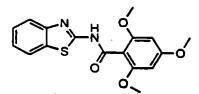
59-0197

Max: 162 % EC50: 150 nM



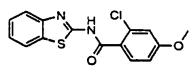
59-0202

Max: 155 % EC50: 150 nM



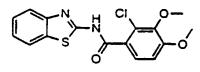
59-0204

Max: 70 % EC50: 50 nM



59-0205

Max: 250 % EC50: < 0.8 nM



59-0206

Max: 150 % EC50: 20 nM S CI

59-0207

Max: 50 % EC50: 100 nM

59-0208

Max: 85 % EC50: 1 uM

FIG. 50

50-0197 Max: 245 % EC50: 3 nM

59-0078 Max: 380 % EC50: 1 nM

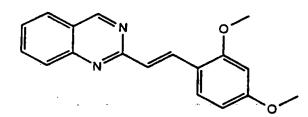
FIG. 6A-

59-0199

Max: 170 % EC50: 100 nM

59-0203

Max: 275 % EC50: <1 nM



59-0286

Max: 160 % EC50: 300 nM

59-0285

Max: 200 % EC50: 30 nM

FIG. 6B

R =



59-0030 Max: 90 % EC50: 1 uM



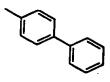
59-0089 Max: 120 % EC50: 5 uM



59-0093 Max: 35 %



59-0094 Max: 45 %



59-0091 Max: 96 % EC50: 1 uM



59-0090 Max: 41 %

111



59-0092 Max: 50 % EC50: 10 uM



59-0150 Max: 500 % EC50: 1 nM



59-0199 Max: 170 % EC50: 100 nM



59-0198 Max: 135 % EC50: 100 nM

FIG.

59-0145

Max: 300 % EC50: 0.5 uM

59-0450

Max: 270 % EC50: 5 uM

59-0483

Max: 260 % EC50: 3 uM

7

59-0459

Max: 180 % EC50: 5 uM

59-0480

Max: 180 % EC50: 5 uM

FIG.

FIG. 8 #

FIG.

59-0098

X, Y = F, Cl, OMe < 50 % max @ 100 uM

59-0098 Analogs

X, Y = F, Cl, OMe < 50 % max @ 100 uM

59-0096 Analogs

X, Y = F, Cl, OMe < 50 % max @ 100 uM

59-0097 Analogs

8C

FIG.

Score

			Max	ZGI Score in	OS Sereen
	Compound		Response of	Ex Vivo	in Ex Vivo
Compoun	<u>Class</u>	EC50	<u>59-0008</u>	Assay	Assay
59-0364	Р	0	0	1	
59-0076	Р	0	0	1	
59-0451	Р	0	0	1	
59-0472	P	0	0	1	
59-0073	Р	0	0		1+
59-0095	Н	??	0.5x (30 uM)		1
59-0471	Р	??	0.5x (100 uM)	1	·
59-0030	Q	??	.7x ( 1uM)	1 1	1,1+
59-0470	P	50 uM	1.2x (100 uM)	1 1	,,,,,
59-0450	Р	5 uM	2.7x (30 uM)	·	
59-0459	Р	5 uM	2x (10 uM)	1	
59-0064	Q	3 uM	1.5x (? uM)	1	ļ

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59-0008	Q	1 uM			1
Siego Lia		Cleiche Me	TAIN (SIEW)	<b>******</b>	
59-0106	T	300 nM	2x (9 uM)		1
59-0070	T	200nM	2x (3 uM)		1,1+
59-0097	Н	100 nM?	2x (30 uM)		1+
59-0096	Н	100 nM?	4x (100 uM)		1
59-0116	н	30 nM	2.5x (3 uM)		1+,2-
59-0210	Ţ	30 nM	2x (3 uM)		1
F9:0005		2/8/2017/	MAINS SASSES		2.5
59-0019	Q	10 nM	2.5x (300 nM)	1+,2-	1,1+
59-0078	Q	9 nM	4x (1 uM)		1
59-0045	Н	5 nM	4x (1uM)	1	1
50-0197	Q	3 nM	2.5x (300 nM)	1	1+,2-
59-0099	T	2 nM?	3x (1 uM)		1,1+
59-0282	Q	1 nM	2x (3 uM)		1+,2-
50F020E		PYME	20(651)//1		
59-0072	Т	300 pM	2x (uM)	1-1+	1,1+
59-0150	Q	<1 nM	5x (3 uM)	1-2?	1
59-0104	T	<1 nM	2x (uM)	1+,2-	. 1
59-0103	T	<1 nM	2x (30 nM)	·	1,1+
59-0124	T	<1 nM	2.5x (1 uM)		1+,2-
59-0205	T	<1 nM	2x (2 nM)		1

T = Benzothiazole (104)

H = Hydrazone/Hydrazide (45) Q = Quinotine/Quinoxaline (197) P = Bis-pyridines (145)

Figure 9

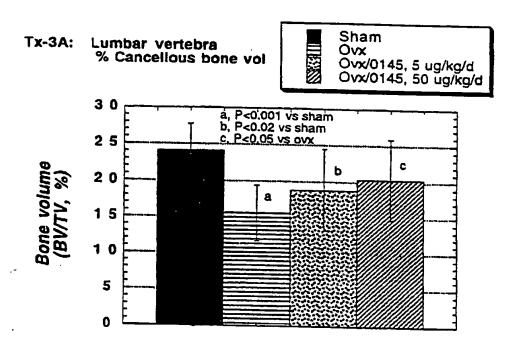
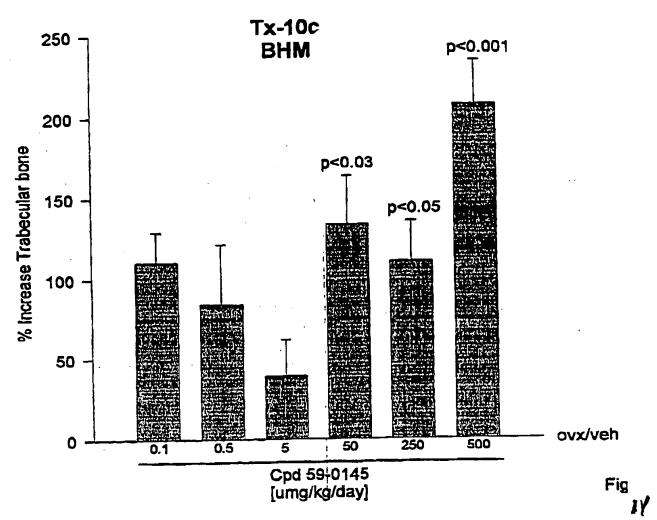


Fig 10



% Increase of trabecular bone over the ovx/vehicle group

Tx-10c

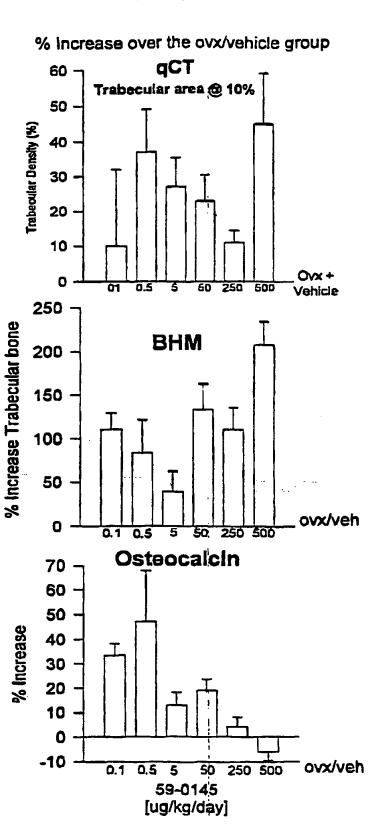


Fig 12

MOLSTRUCTURE	MOL>NNC MOL WEIGHT NUM1		
	59-0020	266.732	
	59-0021	284.723	
	59-0022	266.367	
00	59-0023	239.276	
C S L N S N C	59-0008	254.315	
	59-0024	220.276	
a _a	59-0025	224.308	
	59-0026	248.29	
حفر	59-0027	250.303	
O. O. O.	59-0028	226.283	
منان	59-0029	249.272	

	50.000		
	59-0031	231.3	
	i	į	
	59-0030	233.275	
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International application No. PCT/US97/18864

A. CLA	SSIFICATION OF SUBJECT MATTER		
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	US CL: Please See Extra Sheet.		
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B. FIELDS SEARCHED			
Minimum d	ocumentation searched (classification system follow	red by classification symbols)	
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	CUMENTS CONSIDERED TO BE RELEVANT		
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Category*	Citation of document, with indication, where	appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,441,964 A (BRYANT et al.) document.	15 August 1995, see entire	1-2, 5-28, 55-56
Y	US 5,523,309 A (BRYANT et al.)	04 June 1996, see entire	1-2, 5-28, 55-56
	document, especially claim 8.		
Y,P	US 5,622,974 A (MUEHL) 22 Apr	il 1997, see entire document	1-2 5-28 55-56
	especially claim 5.	ii 2227, see enime deciment,	1 2, 3 20, 33 30
Y	WO 93/10113 A1 (TEIKOKU HORN	MONE MFG. CO., LTD.) 27	1-2, 5-28, 55-56
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Y	WO 05/10513 A1 (DEIZED INC.)	20 April 1005	10 500 5550
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	document, especially claim 20.		
Y	US 5,280,040 A (LABROO et al.)	18 January 1994, see entire	1-4, 31-43, 55-56
	document.	, , , , , , , ,	1 1,51 15,55 50
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X Furth	er documents are listed in the continuation of Box	C. See patent family annex.	
Spe	scial categories of cited documents:	°T° later document published after the inte	mational filing date or priority
	A" document defining the general state of the art which is not considered to be of particular relevance date and not in conflict with the application but cited to understand the principle or theory underlying the invention		
"R. ceri	lier document published on or after the international filing date	"X" document of particular relevance; the considered novel or cannot be consider	claimed invention cannot be
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mer	ument referring to an oral disclosure, use, exhibition or other uns	combined with one or more other such being obvious to a person skilled in th	documents, such combination
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International application No. PCT/US97/18864

	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Reference Chair 110
Y	Chem. abstr. Vol. 127, abstract No. 127:17703, PETRIE et al. 'Preparation of (hetero) aromatic compounds for treating bone deficit conditions', WO-97/15308 (Eng.).	1-4, 31-43, 55-56
Y	Chem. abstr. Vol. 107, abst. No. 107:109578, WATTS et al. 'Studies on the ligand specificity and potential identity of microsomal antiestrogen-binding sites', Mol. Pharmocol. 1987, 31(5), 541-51.	1-2, 50-56
Y	Chem. abstr. Vol. 108, abstract No. 108:69162, JORDAN et al. 'Effects of antiestrogens on bone in castrated and intact female rats', Breast Cancer Res. Treat. 1987, 10(1), 31-5.	1-2, 50-56
Y	Chem. abstr. Vol. 115, abstract No. 115:8533, SCHWARZ et al. '1,2-diphenyl-1-pyridybut-1-enes - potential antiestrogens. part 1. synthesis' Arch. Pharm. 1991, 324(4), 223-9.	1-2, 44-49, 55-56
Y	NEELAM et al. Structure-activity relationship of antiestrogens: A	1-2, 50-56
1	study using triarylbutenone, benzofuran and triayrlfuran analogues as models for triarylethylenes and triarylpropenones. J. Med. chem. 1989, Vol. 32, pages 1700-1707, see entire article.	
Y	study using triarylbutenone, benzofuran and triayrlfuran analogues as models for triarylethylenes and triarylpropenones. J. Med.	1-2, 5-28, 55-56
	study using triarylbutenone, benzofuran and triayrlfuran analogues as models for triarylethylenes and triarylpropenones. J. Med. chem. 1989, Vol. 32, pages 1700-1707, see entire article. VON ANGERER et al. Studies on heterocycle-based pure estrogen antagonists. Ann. N. Y. Academy Sciences. 1995, Vol.	
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Form PCT/ISA/210 (continuation of second sheet)(July 1992)*

International application No. PCT/US97/18864

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)
This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:
1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).
Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)
This International Searching Authority found multiple inventions in this international application, as follows:
Please See Extra Sheet.
1. X As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
Remark on Protest The additional search fees were accompanied by the applicant's protest. No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet(1))(July 1992)★

International application No. PCT/US97/18864

A. CLASSIFICATION OF SUBJECT MATTER:

IPC (6): A61K 31/165, 31/215, 31/33, 31/405, 31/415, 31/42, 31/425, 31/44, 31/47, 31/505, 31/53, 31/535, 31/54

A. CLASSIFICATION OF SUBJECT MATTER:

US CL: 514/222.5, 223.2, 223.8, 224.2, 226.5, 229.2, 230.5, 255, 258, 259, 296, 307, 311, 336, 345, 352, 354, 457, 365, 367, 374, 375, 385, 394, 396, 397, 415, 443, 535, 646

B. FIELDS SEARCHED

Minimum documentation searched Classification System: U.S.

514/222.5, 223.2, 223.8, 224.2, 226.5, 229.2, 230.5, 255, 258, 259, 296, 307, 311, 336, 345, 352, 354, 457, 365, 367, 374, 375, 385, 394, 396, 397, 415, 443, 535, 646

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING This ISA found multiple inventions as follows:

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack Unity of Invention because they are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for more than one species to be searched, the appropriate additional search fees must be paid. The claims are deemed to correspond to the species as listed in the following manner:

Group I, claims 3-4 and 31-43 compounds corresponding to Ar1 is condensed six membered heterocyclic ring, Ar2 is various aromatic rings;

Group II, claims 5-28, compounds corresponding to Ar1 is condensed five membered heterocyclic ring, Ar2 is various aromatic rings;

Group III, claims 29-30, compounds corresponding to Ar1 is isolated five membered heterocyclic ring, Ar2 is various aromatic rings;

Group IV, claims 44-49, compounds corresponding to Ar1 is isolated six membered heterocyclic ring, Ar2 is various aromatic rings;

Group V, claims 50-54, compounds corresponding to Ar1 is phenyl ring, Ar2 is various aromatic rings;

claims 1-2, 55-56 in part (remaining compounds) Group IV.

The following claims are generic: 1-2, 55-56

The species listed above do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2 and ANNEX B section (f), the species lack the same or corresponding special technical features for the following reasons:

The six groups of compounds corresponding to method of treating conditions of deficiency in bone growth, resorption or replacement using structurally distinctive compounds. Each group of compounds as delineated above does not share significant structural element (see Ar1, Ar2 and L are all variables, thus, not common element). In addition, at least one Markush alternative is found in CA 127:17703.

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(51) International Patent Classification ⁶:

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(54) Title: COMPOSITIONS AND METHODS FOR TREATING BONE DEFICIT CONDITIONS

(57) Abstract

Compounds containing two aromatic systems covalently linked through a linker containing one or more atoms, or "linker" defined as including a covalent bond *per se* so as to space the aromatic systems at a distance 1.5–15Å, are effective in treating conditions associated with bone deficits. The compounds can be administered to vertebrate subjects alone or in combination with additional agents that promote bone growth or that inhibit bone resorption. They can be screened for activity prior to administration by assessing their ability to effect the transcription of a reporter gene coupled to a promoter associated with a bone morphogenetic protein and/or their ability to stimulate calvarial growth in model animal systems.

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COMPOSITIONS AND METHODS FOR TREATING BONE DEFICIT CONDITIONS

Technical Field

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The invention relates to compositions and methods for use in limiting undesired bone loss in a vertebrate at risk of such bone loss, in treating conditions that are characterized by undesired bone loss or by the need for bone growth, in treating fractures, and in treating cartilage disorders. More specifically, the invention concerns the use of specific classes of compounds identified or characterized by a high throughput screening assay.

Background Art

Bone is not a static tissue. It is subject to constant breakdown and resynthesis in a complex process mediated by osteoblasts, which produce new bone, and osteoclasts, which destroy bone. The activities of these cells are regulated by a large number of cytokines and growth factors, many of which have now been identified and cloned. Mundy has described the current knowledge related to these factors (Mundy, G.R. Clin Orthop 324:24-28, 1996; Mundy, G.R. J Bone Miner Res 8:S505-10, 1993).

Although there is a great deal of information available on the factors which influence the breakdown and resorption of bone, information on growth factors which stimulate the formation of new bone is more limited. Investigators have searched for sources of such activities, and have found that bone tissue itself is a storehouse for factors which have the capacity for stimulating bone cells. Thus, extracts of bovine bone tissue obtained from slaughterhouses contain not only structural proteins which are responsible for maintaining the structural integrity of bone, but also biologically active bone growth factors which can stimulate bone cells to proliferate. Among these latter factors are transforming growth factor β , the heparin-binding growth factors (acidic and basic fibroblast growth factor), the insulin-like growth factors (insulin-like growth factor I and insulin-like growth factor II), and a recently described family of

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proteins called bone morphogenetic proteins (BMPs). All of these growth factors have effects on other types of cells, as well as on bone cells.

The BMPs are novel factors in the extended transforming growth factor ß superfamily. They were first identified by Wozney J. et al. Science (1988) 242:1528-34, using gene cloning techniques, following earlier descriptions characterizing the biological activity in extracts of demineralized bone (Urist M. Science (1965) 150:893-99). Recombinant BMP2 and BMP4 can induce new bone formation when they are injected locally into the subcutaneous tissues of rats (Wozney J. Molec Reprod Dev (1992) 32:160-67). These factors are expressed by normal osteoblasts as they differentiate, and have been shown to stimulate osteoblast differentiation and bone nodule formation in vitro as well as bone formation in vivo (Harris S. et al. J. Bone Miner Res (1994) 9:855-63). This latter property suggests potential usefulness as therapeutic agents in diseases which result in bone loss.

The cells which are responsible for forming bone are osteoblasts. As osteoblasts differentiate from precursors to mature bone-forming cells, they express and secrete a number of enzymes and structural proteins of the bone matrix, including Type-1 collagen, osteocalcin, osteopontin and alkaline phosphatase (Stein G. et al. Curr Opin Cell Biol (1990) 2:1018-27; Harris S. et al. (1994), supra). They also synthesize a number of growth regulatory peptides which are stored in the bone matrix, and are presumably responsible for normal bone formation. These growth regulatory peptides include the BMPs (Harris S. et al. (1994), supra). In studies of primary cultures of fetal rat calvarial osteoblasts, BMPs 1, 2, 3, 4, and 6 are expressed by cultured cells prior to the formation of mineralized bone nodules (Harris S. et al. (1994), supra). Like alkaline phosphatase, osteocalcin and osteopontin, the BMPs are expressed by cultured osteoblasts as they proliferate and differentiate.

Although the BMPs are potent stimulators of bone formation in vitro and in vivo, there are disadvantages to their use as therapeutic agents to enhance bone healing. Receptors for the bone morphogenetic proteins have been identified in many tissues, and the BMPs themselves are expressed in a large variety of tissues in specific temporal and spatial patterns. This suggests that BMPs may have effects on many

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tissues other than bone, potentially limiting their usefulness as therapeutic agents when administered systemically. Moreover, since they are peptides, they would have to be administered by injection. These disadvantages impose severe limitations to the development of BMPs as therapeutic agents.

There is a plethora of conditions which are characterized by the need to enhance bone formation. Perhaps the most obvious is the case of bone fractures, where it would be desirable to stimulate bone growth and to hasten and complete bone repair. Agents that enhance bone formation would also be useful in facial reconstruction procedures. Other bone deficit conditions include bone segmental defects, periodontal disease, metastatic bone disease, osteolytic bone disease and conditions where connective tissue repair would be beneficial, such as healing or regeneration of cartilage defects or injury. Also of great significance is the chronic condition of osteoporosis, including age-related osteoporosis and osteoporosis associated with postmenopausal hormone status. Other conditions characterized by the need for bone growth include primary and secondary hyperparathyroidism, disuse osteoporosis, diabetes-related osteoporosis, and glucocorticoid-related osteoporosis. In addition, or alternatively, the compounds of the present invention may modulate metabolism, proliferation and/or differentiation of normal or aberrant cells or tissues.

There are currently no satisfactory pharmaceutical approaches to managing any of these conditions. Bone fractures are still treated exclusively using casts, braces, anchoring devices and other strictly mechanical means. Further bone deterioration associated with postmenopausal osteoporosis has been decreased or prevented with estrogens or bisphosphonates.

US Patent 5, 280, 040 discloses a class of compounds which are 3, 4-diaryl chromans. These compounds can be considered derivatives of 2,3,4 triphenyl butanol, where the hydroxy at the 1-position forms an ether with the ortho position of the phenyl group substituted at the 4-position of the butanol. The parent 3,4-diaryl chromans do not contain nitrogen atoms in the aromatic moieties or their linkers. A preferred compound, centchroman, contains a nitrogen substituent only in one of the

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substituents on a phenyl moiety. These compounds are disclosed in the '040 patent as useful in the treatment of osteoporosis.

In addition, the PCT application WO97/15308 published 1 May 1997 describes a number of classes of compounds that are active in the screening assay described below and are useful in treating bone disorders. These compounds, generically, are of the formulae

$$R^{a}_{m} \xrightarrow{Z}_{L-Ar^{2}}$$

wherein R² is a non-interfering substituent;

m is an integer of 0-4;

each dotted line represents an optional π -bond;

each Z is independently N, NR, O, S, CR or CR₂, where each R is independently H or alkyl (1-6C);

X is O, S, SO or SO_2 ;

L is a flexible linker; and

Ar² is a substituted or unsubstituted 6-membered aromatic ring; or:

wherein R^a is a non-interfering substituent;

n is an integer of 0 and 5;

L is a flexible linker which does not contain nitrogen or is a constrained linker, and

Ar² is a substituted or unsubstituted phenyl or a substituted or unsubstituted naphthyl.

There remains a need for additional compositions which can ameliorate the effects of abnormalities in bone formation or resorption. The present invention

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expands the repertoire of compounds useful for limiting or treating bone deficit conditions, and for other uses that should be apparent to those skilled in the art from the teachings herein.

5 Disclosure of the Invention

The invention provides compounds that can be administered as ordinary pharmaceuticals and have the metabolic effect of enhancing bone growth or inhibiting resorption. The compounds of the invention can be identified using an assay for their ability to activate control elements associated with bone anabolic factors. Thus, the invention is directed to methods and compositions for treating bone disorders, which methods and compositions use, as active ingredients, compounds wherein two aromatic systems are coupled so as to be spaced apart from each other by about 1.5 to about 15 Angstroms. The thus-linked systems (including the linker coupling them) preferably include at least one nitrogen atom.

Therefore, the compounds useful in the invention can be described as having the formula Ar¹-linker-Ar², wherein each of Ar¹ and Ar² is independently an aromatic system and the linker portion of the formula spaces Ar¹ and Ar² apart by a distance of approximately 1.5-15 Angstroms. Ar¹, Ar² and the linker may optionally be substituted with non interfering substituents. In the useful compounds, there is preferably at least one nitrogen atom in either Ar¹, Ar² and/or the linker, independent of any substituents thereon. Preferably, the compounds of the invention contain at least one additional heteroatom selected from the group consisting of N, S and O, independent of any substituent.

Thus, in one aspect, the invention is directed to a method to treat a condition in a vertebrate animal characterized by a deficiency in, or need for, bone growth replacement and/or an undesirable level of bone resorption, which method comprises administering to a vertebrate subject in need of such treatment an effective amount of certain compounds of the formula:

wherein each of Ar¹ and Ar² is independently substituted or unsubstituted phenyl, substituted or unsubstituted naphthyl, a substituted or unsubstituted aromatic system containing a 6-membered heterocycle, or a substituted or unsubstituted aromatic system containing a 5-membered heterocycle; and

L is a linker that provides spacing of 1.5-15Å.

In other aspects, the invention relates to pharmaceutical compositions for use in the method, and to the compounds for use in preparing a medicament for use in the method.

10 Brief Description of the Drawings

Figure 1 gives a schematic representation of the compounds used as active ingredients in the methods and compositions of the invention.

Figure 2 shows the dose response curve for a positive control compound, designated 59-0008.

Figures 3 and 4 show illustrative compounds of the invention and the results obtained with them in an *in vitro* test for stimulation of bone growth.

Figures 5A, 5B and 5C show structures and results of a screening assay for a group of compounds which varies the parameters of lead compound 59-0072.

Figures 6A, 6B and 6C show structures and results of a screening assay for a group of compounds which varies the parameters of lead compound 50-0197.

Figure 7 shows structures and results of a screening assay for a group of compounds which varies the parameters of lead compound 59-0145.

Figures 8A, 8B and 8C show structures and results of a screening assay for a group of compounds which varies the parameters of lead compound 59-0045.

Figure 9 shows the results in an *ex vivo* calvarial assay for various compunds of the invention.

Figure 10 shows the increase in bone volume effected by subcutaneous administration of compound 59-0145 in the OVX in vivo assay.

Figure 11 is a graphical representation of percent increase in trabecular bone in ovariectomized rats treated with compound 59-0145.

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Figure 12 presents graphs showing results of qCT and bone histomorphometri and serum osteocalcin levels in rats treated with compound 59-0145.

Figure 13 (41 pages) is a list of compounds used in screening for bone morphogenic activity according to the screening assay set forth herein.

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Modes of Carrying Out the Invention

A rapid throughput screening test for compounds capable of stimulating expression of a reporter gene linked to a BMP promoter (a surrogate for the production of bone morphogenetic factors that are endogenously produced) is described in WO96/38590 published 5 December 1996, the contents of which are incorporated herein by reference. This assay is also described as a portion of a study of immortalized murine osteoblasts (derived from a mouse expressing a transgene composed of a BMP2 promoter driving expression of T-antigen) in Ghosh-Choudhery, N. et al. Endocrinology (1996) 137:331-39. In this study, the immortalized cells were stably transfected with a plasmid containing a luciferase reporter gene driven by a mouse BMP2 promoter (-2736/114 bp), and responded in a dose-dependent manner to recombinant human BMP2.

Briefly, the assay utilizes cells transformed permanently or transiently with constructs in which the promoter of a bone morphogenetic protein, specifically BMP2 or BMP4, is coupled to a reporter gene, typically luciferase. These transformed cells are then evaluated for the production of the reporter gene product; compounds that activate the BMP promoter will drive production of the reporter protein, which can be readily assayed. Over 40,000 compounds have been subjected to this rapid screening technique, and only a very small percentage are able to elicit a level of production of luciferase 5-fold greater than that produced by vehicle. Compounds that activate the BMP promoter share certain structural characteristics not present in inactive compounds. The active compounds ("BMP promoter-active compounds" or "active compounds") are useful in promoting bone or cartilage growth, and thus in the treatment of vertebrates in need of bone or cartilage growth.

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BMP promoter-active compounds can be examined in a variety of other assays that test specificity and toxicity. For instance, nonBMP promoters or response elements can be linked to a reporter gene and inserted into an appropriate host cell. Cytotoxicity can be determined by visual or microscopic examination of BMP promoter- and/or nonBMP promoter-reporter gene-containing cells, for instance. Alternatively, nucleic acid and/or protein synthesis by the cells can be monitored. For in vivo assays, tissues may be removed and examined visually or microscopically, and optionally examined in conjunction with dyes or stains that facilitate histologic examination. In assessing in vivo assay results, it may also be useful to examine biodistribution of the test compound, using conventional medicinal chemistry/animal model techniques.

As used herein, "limit" or "limiting" and "treat" or "treatment" are interchangeable terms. The terms include a postponement of development of bone deficit symptoms and/or a reduction in the severity of such symptoms that will or are expected to develop. The terms further include ameliorating existing bone or cartilage deficit symptoms, preventing additional symptoms, ameliorating or preventing the underlying metabolic causes of symptoms, preventing or reversing bone resorption and/or encouraging bone growth. Thus, the terms denote that a beneficial result has been conferred on a vertebrate subject with a cartilage, bone or skeletal deficit, or with the potential to develop such deficit.

By "bone deficit" is meant an imbalance in the ratio of bone formation to bone resorption, such that, if unmodified, the subject will exhibit less bone than desirable, or the subject's bones will be less intact and coherent than desired. Bone deficit may also result from fracture, from surgical intervention or from dental or periodontal disease. By "cartilage defect" is meant damaged cartilage, less cartilage than desired, or

By "cartilage defect" is meant damaged cartilage, less cartilage than desired, or cartilage that is less intact and coherent than desired.

Representative uses of the compounds of the present invention include: repair of bone defects and deficiencies, such as those occurring in closed, open and nonunion fractures; prophylactic use in closed and open fracture reduction; promotion of bone healing in plastic surgery; stimulation of bone ingrowth into noncemented prosthetic

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joints and dental implants; elevation of peak bone mass in premenopausal women; treatment of growth deficiencies; treatment of peridontal disease and defects, and other tooth repair processes; increase in bone formation during distraction osteogenesis; and treatment of other skeletal disorders, such as age-related osteoporosis, postmenopausal osteoporosis, glucocorticoid-induced osteoporosis or disuse osteoporosis and arthritis. The compounds of the present invention can also be useful in repair of congenital, trauma-induced or surgical resection of bone (for instance, for cancer treatment), and in cosmetic surgery. Further, the compounds of the present invention can be used for limiting or treating cartilage defects or disorders, and may be useful in wound healing or tissue repair.

Bone or cartilage deficit or defect can be treated in vertebrate subjects by administering compounds of the invention which have been identified through suitable. screening assays and which exhibit certain structural characteristics. The compositions of the invention may be administered systemically or locally. For systemic use, the compounds herein are formulated for parenteral (e.g., intravenous, subcutaneous, intramuscular, intraperitoneal, intranasal or transdermal) or enteral (e.g., oral or rectal) delivery according to conventional methods. Intravenous administration will be by a series of injections or by continuous infusion over an extended period. Administration by injection or other routes of discretely spaced administration will generally be performed at intervals ranging from weekly to once to three times daily. Alternatively, the compounds disclosed herein may be administered in a cyclical manner (administration of disclosed compound; followed by no administration; followed by administration of disclosed compound, and the like). Treatment will continue until the desired outcome is achieved. In general, pharmaceutical formulations will include a compound of the present invention in combination with a pharmaceutically acceptable vehicle, such as saline, buffered saline, 5% dextrose in water, borate-buffered saline containing trace metals or the like. Formulations may further include one or more excipients, preservatives, solubilizers, buffering agents, albumin to prevent protein loss on vial surfaces, lubricants, fillers, stabilizers, etc. Methods of formulation are well known in the art and are disclosed, for example, in Remington's Pharmaceutical

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Sciences, Gennaro, ed., Mack Publishing Co., Easton PA, 1990, which is incorporated herein by reference. Pharmaceutical compositions for use within the present invention can be in the form of sterile, nonpyrogenic liquid solutions or suspensions, coated capsules, suppositories, lyophilized powders, transdermal patches or other forms known in the art. Local administration may be by injection at the site of injury or defect, or by insertion or attachment of a solid carrier at the site, or by direct, topical application of a viscous liquid. For local administration, the delivery vehicle preferably provides a matrix for the growing bone or cartilage, and more preferably is a vehicle that can be absorbed by the subject without adverse effects.

Delivery of compounds herein to wound sites may be enhanced by the use of controlled-release compositions, such as those described in WIPO publication WO 93/20859, which is incorporated herein by reference in its entirety. Films of this type are particularly useful as coatings for prosthetic devices and surgical implants. The films may, for example, be wrapped around the outer surfaces of surgical screws, rods, pins, plates and the like. Implantable devices of this type are routinely used in orthopedic surgery. The films can also be used to coat bone filling materials, such as hydroxyapatite blocks, demineralized bone matrix plugs, collagen matrices and the like. In general, a film or device as described herein is applied to the bone at the fracture site. Application is generally by implantation into the bone or attachment to the surface using standard surgical procedures.

In addition to the copolymers and carriers noted above, the biodegradable films and matrices may include other active or inert components. Of particular interest are those agents that promote tissue growth or infiltration, such as growth factors. Exemplary growth factors for this purpose include epidermal growth factor (EGF), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), transforming growth factors (TGFs), parathyroid hormone (PTH), leukemia inhibitory factor (LIF), and insulin-like growth factors (IGFs). Agents that promote bone growth, such as bone morphogenetic proteins (U.S. Patent No. 4,761,471; PCT Publication WO 90/11366), osteogenin (Sampath et al. Proc. Natl. Acad. Sci. USA (1987) 84:7109-13) and NaF (Tencer et al. J. Biomed. Mat. Res. (1989) 23: 571-89) are also preferred.

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Biodegradable films or matrices include calcium sulfate, tricalcium phosphate, hydroxyapatite, polylactic acid, polyanhydrides, bone or dermal collagen, pure proteins, extracellular matrix components and combinations thereof. Such biodegradable materials may be used in combination with nonbiodegradable materials, to provide desired mechanical, cosmetic or tissue or matrix interface properties.

Alternative methods for delivery of compounds of the present invention include use of ALZET osmotic minipumps (Alza Corp., Palo Alto, CA); sustained release matrix materials such as those disclosed in Wang et al. (PCT Publication WO 90/11366); electrically charged dextran beads, as disclosed in Bao et al. (PCT Publication WO 92/03125); collagen-based delivery systems, for example, as disclosed in Ksander et al. Ann. Surg. (1990) 211(3):288-94; methylcellulose gel systems, as disclosed in Beck et al. J. Bone Min. Res. (1991) 6(11):1257-65; and alginate-based systems, as disclosed in Edelman et al. Biomaterials (1991) 12:619-26. Other methods well known in the art for sustained local delivery in bone include porous coated metal protheses that can be impregnated and solid plastic rods with therapeutic compositions incorporated within them.

The compounds of the present invention may also be used in conjunction with agents that inhibit bone resorption. Antiresorptive agents, such as estrogen, bisphosphonates and calcitonin, are preferred for this purpose. More specifically, the compounds disclosed herein may be administered for a period of time (for instance, months to years) sufficient to obtain correction of a bone deficit condition. Once the bone deficit condition has been corrected, the vertebrate can be administered an anti-resorptive compound to maintain the corrected bone condition. Alternatively, the compounds disclosed herein may be administered with an anti-resorptive compound in a cyclical manner (administration of disclosed compound, followed by anti-resorptive, followed by disclosed compound, and the like).

In additional formulations, conventional preparations such as those described below may be used.

Aqueous suspensions may contain the active ingredient in admixture with pharmacologically acceptable excipients, comprising suspending agents, such as methyl

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cellulose; and wetting agents, such as lecithin, lysolethicin or long-chain fatty alcohols. The said aqueous suspensions may also contain preservatives, coloring agents, flavoring agents and sweetening agents in accordance with industry standards.

Preparations for topical and local application comprise aerosol sprays, lotions, gels and ointments in pharmaceutically appropriate vehicles which may comprise lower aliphatic alcohols, polyglycols such as glycerol, polyethylene glycol, esters of fatty acids, oils and fats, and silicones. The preparations may further comprise antioxidants, such as ascorbic acid or tocopherol, and preservatives, such as p-hydroxybenzoic acid esters.

Parenteral preparations comprise particularly sterile or sterilized products.

Injectable compositions may be provided containing the active compound and any of the well known injectable carriers. These may contain salts for regulating the osmotic pressure.

If desired, the osteogenic agents can be incorporated into liposomes by any of
the reported methods of preparing liposomes for use in treating various pathogenic
conditions. The present compositions may utilize the compounds noted above
incorporated in liposomes in order to direct these compounds to macrophages,
monocytes, other cells and tissues and organs which take up the liposomal
composition. The liposome-incorporated compounds of the invention can be utilized
by parenteral administration, to allow for the efficacious use of lower doses of the
compounds. Ligands may also be incorporated to further focus the specificity of the
liposomes.

Suitable conventional methods of liposome preparation include, but are not limited to, those disclosed by Bangham, A.D. et al. J Mol Biol (1965) 23:238-252, Olson, F. et al. Biochim Biophys Acta (1979) 557:9-23, Szoka, F. et al. Proc Natl Acad Sci USA (1978) 75:4194-4198, Mayhew, E. et al. (1984) 775:169-175, Kim, S. et al. Biochim Biophys Acta (1983) 728:339:348, and Mayer, et al. Biochim Biophys Acta (1986) 858:161-168.

The liposomes may be made from the present compounds in combination with any of the conventional synthetic or natural phospholipid liposome materials including

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phospholipids from natural sources such as egg, plant or animal sources such as phosphatidylcholine, phosphatidylethanolamine, phosphatidylglycerol, sphingomyelin, phosphatidylserine, or phosphatidylinositol. Synthetic phospholipids that may also be used, include, but are not limited to: dimyristoylphosphatidylcholine,

- dioleoylphosphatidylcholine, dipalmitoylphosphatidylcholine and distearoylphosphatidycholine, and the corresponding synthetic phosphatidylethanolamines and phosphatidylglycerols. Cholesterol or other sterols, cholesterol hemisuccinate, glycolipids, cerebrosides, fatty acids, gangliosides, sphingolipids, 1,2-bis(oleoyloxy)-3-(trimethyl ammonio) propane (DOTAP), N-[1 (2,3-dioleoyl) propyl-N,N,N-trimethylammonium chloride (DOTMA), and other cationic lipids may be incorporated into the liposomes, as is known to those skilled in the art. The relative amounts of phospholipid and additives used in the liposomes may be varied if desired. The preferred ranges are from about 60 to 90 mole percent of the
 - phospholipid; cholesterol, cholesterol hemisuccinate, fatty acids or cationic lipids may be used in amounts ranging from 0 to 50 mole percent. The amounts of the present compounds incorporated into the lipid layer of liposomes can be varied with the concentration of their lipids ranging from about 0.01 to about 50 mole percent.

Using conventional methods, approximately 20 to 30% of the compound present in solution can be entrapped in liposomes; thus, approximately 70 to 80% of the active compound is wasted. In contrast, where the compound is incorporated into liposomes, virtually all of the compound is incorporated into the liposome, and essentially none of the active compound is wasted.

The liposomes with the above formulations may be made still more specific for their intended targets with the incorporation of monoclonal antibodies or other ligands specific for a target. For example, monoclonal antibodies to the BMP receptor may be incorporated into the liposome by linkage to phosphatidylethanolamine (PE) incorporated into the liposome by the method of Leserman, L. et al. Nature (1980) 288:602-604.

Veterinary uses of the disclosed compounds are also contemplated. Such uses would include limitation or treatment of bone or cartilage deficits or defects in

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domestic animals, livestock and thoroughbred horses. The compounds described herein can also modify a target tissue or organ environment, so as to attract bone-forming cells to an environment in need of such cells.

The compounds of the present invention may also be used to stimulate growth of bone-forming cells or their precursors, or to induce differentiation of bone-forming cell precursors, either in vitro or ex vivo. As used herein, the term "precursor cell" refers to a cell that is committed to a differentiation pathway, but that generally does not express markers or function as a mature, fully differentiated cell. As used herein, the term "mesenchymal cells" or "mesenchymal stem cells" refers to pluripotent progenitor cells that are capable of dividing many times, and whose progeny will give rise to skeletal tissues, including cartilage, bone, tendon, ligament, marrow stroma and connective tissue (see A. Caplan J. Orthop. Res. (1991) 9:641-50). As used herein, the term "osteogenic cells" includes osteoblasts and osteoblast precursor cells. More particularly, the disclosed compounds are useful for stimulating a cell population containing marrow mesenchymal cells, thereby increasing the number of osteogenic cells in that cell population. In a preferred method, hematopoietic cells are removed from the cell population, either before or after stimulation with the disclosed compounds. Through practice of such methods, osteogenic cells may be expanded. The expanded osteogenic cells can be infused (or reinfused) into a vertebrate subject in need thereof. For instance, a subject's own mesenchymal stem cells can be exposed to compounds of the present invention ex vivo, and the resultant osteogenic cells could be infused or directed to a desired site within the subject, where further proliferation and/or differentiation of the osteogenic cells can occur without immunorejection. Alternatively, the cell population exposed to the disclosed compounds may be immortalized human fetal osteoblastic or osteogenic cells. If such cells are infused or implanted in a vertebrate subject, it may be advantageous to "immunoprotect" these nonself cells, or to immunosuppress (preferably locally) the recipient to enhance transplantation and bone or cartilage repair.

Within the present invention, an "effective amount" of a composition is that amount which produces a statistically significant effect. For example, an "effective

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amount" for therapeutic uses is the amount of the composition comprising an active compound herein required to provide a clinically significant increase in healing rates in fracture repair; reversal of bone loss in osteoporosis; reversal of cartilage defects or disorders; prevention or delay of onset of osteoporosis; stimulation and/or augmentation of bone formation in fracture nonunions and distraction osteogenesis; increase and/or acceleration of bone growth into prosthetic devices; and repair of dental defects. Such effective amounts will be determined using routine optimization techniques and are dependent on the particular condition to be treated, the condition of the patient, the route of administration, the formulation, and the judgment of the practitioner and other factors evident to those skilled in the art. The dosage required for the compounds of the invention (for example, in osteoporosis where an increase in bone formation is desired) is manifested as a statistically significant difference in bone mass between treatment and control groups. This difference in bone mass may be seen, for example, as a 5-20% or more increase in bone mass in the treatment group. Other measurements of clinically significant increases in healing may include, for example, tests for breaking strength and tension, breaking strength and torsion, 4-point bending, increased connectivity in bone biopsies and other biomechanical tests well known to those skilled in the art. General guidance for treatment regimens is obtained from experiments carried out in animal models of the disease of interest.

The dosage of the compounds of the invention will vary according to the extent and severity of the need for treatment, the activity of the administered compound, the general health of the subject, and other considerations well known to the skilled artisan. Generally, they can be administered to a typical human on a daily basis on an oral dose of about 0.1 mg/kg-1000 mg/kg, and more preferably from about 1 mg/kg to about 200 mg/kg. The parenteral dose will appropriately be 20-100% of the oral dose.

Screening Assays

The osteogenic activity of the compounds used in the methods of the invention can be verified using *in vitro* screening techniques, such as the assessment of

transcription of a reporter gene coupled to a bone morphogenetic protein-associated promoter, as described above, or in alternative assays such as the following:

Technique for Neonatal Mouse Calvarial Assay (In vitro)

This assay is similar to that described by Gowen M. & Mundy G. J Immunol (1986) 136:2478-82. Briefly, four days after birth, the front and parietal bones of ICR Swiss white mouse pups are removed by microdissection and split along the sagittal suture. The bones are incubated in BGJb medium (Irvine Scientific, Santa Ana, CA) plus 0.02% (or lower concentration) β-methylcyclodextrin, wherein the medium also contains test or control substances, at 37°C in a humidified atmosphere of 5% CO₂ and 95% air for 96 hours.

Following this, the bones are removed from the incubation media and fixed in 10% buffered formalin for 24-48 hours, decalcified in 14% EDTA for 1 week, processed through graded alcohols; and embedded in paraffin wax. Three µm sections of the calvaria are prepared. Representative sections are selected for histomorphometric assessment of bone formation and bone resorption. Bone changes are measured on sections cut 200 µm apart. Osteoblasts and osteoclasts are identified by their distinctive morphology.

Other auxillary assays can be used as controls to determine nonBMP promoter-mediated effects of test compounds. For example, mitogenic activity can be measured using screening assays featuring a serum-response element (SRE) as a promoter and a luciferase reporter gene. More specifically, these screening assays can detect signalling through SRE-mediated pathways, such as the protein kinase C pathway. For instance, an osteoblast activator SRE-luciferase screen and an insulin mimetic SRE-luciferase screen are useful for this purpose. Similarly, test compound stimulation of cAMP response element (CRE)-mediated pathways can also be assayed. For instance, cells transfected with receptors for PTH and calcitonin (two bone-active agents) can be used in CRE-luciferase screens to detect elevated cAMP levels. Thus, the BMP promoter specificity of a test compound can be examined through use of these types of auxillary assays.

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In vivo Assay of Effects of Compounds on Murine Calvarial Bone Growth Male ICR Swiss white mice, aged 4-6 weeks and weighing 13-26 gm, are employed, using 4-5 mice per group. The calvarial bone growth assay is performed as described in PCT application WO 95/24211. Briefly, the test compound or appropriate control vehicle is injected into the subcutaneous tissue over the right calvaria of normal mice. Typically, the control vehicle is the vehicle in which the compound was solubilized, and is PBS containing 5% DMSO or is PBS containing Tween (2 µl/10 ml). The animals are sacrificed on day 14 and bone growth measured by histomorphometry. Bone samples for quantitation are cleaned from adjacent tissues and fixed in 10% buffered formalin for 24-48 hours, decalcified in 14% EDTA for 1-3 weeks, processed through graded alcohols; and embedded in paraffin wax. Three to five µm sections of the calvaria are prepared, and representative sections are selected for histomorphometric assessment of the effects on bone formation and bone resorption. Sections are measured by using a camera lucida attachment to trace directly the microscopic image onto a digitizing plate. Bone changes are measured on sections cut 200 µm apart, over 4 adjacent 1x1 mm fields on both the injected and noninjected sides of the calvaria. New bone is identified by its characteristic woven structure, and osteoclasts and osteoblasts are identified by their distinctive morphology. Histomorphometry software (OsteoMeasure, Osteometrix, Inc., Atlanta) is used to process digitizer input to determine cell counts and measure areas or perimeters.

Additional In Vivo Assays

Lead compounds can be further tested in intact animals using an *in vivo*, dosing assay. Prototypical dosing may be accomplished by subcutaneous, intraperitoneal or oral administration, and may be performed by injection, sustained release or other delivery techniques. The time period for administration of test compound may vary (for instance, 28 days as well as 35 days may be appropriate). An exemplary, *in vivo* subcutaneous dosing assay may be conducted as follows:

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In a typical study, 70 three-month-old female Sprague-Dawley rats are weight-matched and divided into seven groups, with ten animals in each group. This includes a baseline control group of animals sacrificed at the initiation of the study; a control group administered vehicle only; a PBS-treated control group; and a positive control group administered a compound (nonprotein or protein) known to promote bone growth. Three dosage levels of the compound to be tested are administered to the remaining three groups.

Briefly, test compound, positive control compound, PBS, or vehicle alone is administered subcutaneously once per day for 35 days. All animals are injected with calcein nine days and two days before sacrifice (two injections of calcein administered each designated day). Weekly body weights are determined. At the end of the 35-day cycle, the animals are weighed and bled by orbital or cardiac puncture. Serum calcium, phosphate, osteocalcin, and CBCs are determined. Both leg bones (femur and tibia) and lumbar vertebrae are removed, cleaned of adhering soft tissue, and stored in 70% ethanol for evaluation, as performed by peripheral quantitative computed tomography (pqCT; Ferretti, J. Bone (1995) 17:353S-64S), dual energy X-ray absorptiometry (DEXA; Laval-Jeantet A. et al. Calcif Tissue Intl (1995) 56:14-18; J. Casez et al. Bone and Mineral (1994) 26:61-68) and/or histomorphometry. The effect of test compounds on bone remodeling can thus be evaluated.

Lead compounds also be tested in acute ovariectomized animals (prevention model) using an *in vivo* dosing assay. Such assays may also include an estrogentreated group as a control. An exemplary subcutaneous dosing assay is performed as follows:

In a typical study, 80 three-month-old female Sprague-Dawley rats are weight-matched and divided into eight groups, with ten animals in each group. This includes a baseline control group of animals sacrificed at the initiation of the study; three control groups (sham ovariectomized (sham OVX) + vehicle only; ovariectomized (OVX) + vehicle only; PBS-treated OVX); and a control OVX group that is administered a compound known to promote bone growth. Three dosage levels of the compound to be tested are administered to the remaining three groups of OVX animals.

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Since ovariectomy (OVX) induces hyperphagia, all OVX animals are pair-fed with sham OVX animals throughout the 35 day study. Briefly, test compound, positive control compound, PBS, or vehicle alone is administered subcutaneously once per day for 35 days. Alternatively, test compound can be formulated in implantable pellets that are implanted for 35 days, or may be administered orally, such as by gastric gavage. All animals, including sham OVX/vehicle and OVX/vehicle groups, are injected intraperitoneally with calcein nine days and two days before sacrifice (two injections of calcein administered each designated day, to ensure proper labeling of newly formed bone). Weekly body weights are determined. At the end of the 35-day cycle, the animals' blood and tissues are processed as described above.

Lead compounds may also be tested in chronic OVX animals (treatment model). An exemplary protocol for treatment of established bone loss in ovariectomized animals that can be used to assess efficacy of anabolic agents may be performed as follows. Briefly, 80 to 100 six month old female, Sprague-Dawley rats are subjected to sham surgery (sham OVX) or ovariectomy (OVX) at time 0, and 10 rats are sacrificed to serve as baseline controls. Body weights are recorded weekly during the experiment. After approximately 6 weeks of bone depletion (42 days), 10 sham OVX and 10 OVX rats are randomly selected for sacrifice as depletion period controls. Of the remaining animals, 10 sham OVX and 10 OVX rats are used as placebo-treated controls. The remaining OVX animals are treated with 3 to 5 doses of test drug for a period of 5 weeks (35 days). As a postitive control, a group of OVX rats can be treated with an agent such as PTH, a known anabolic agent in this model (Kimmel et al. Endocrinology (1993) 132:1577-84). To determine effects on bone formation, the following procedure can be followed. The femurs, tibiae and lumbar vertebrae 1 to 4 are excised and collected. The proximal left and right tibiae are used for pqCT measurements, cancellous bone mineral density (BMD) (gravimetric determination), and histology, while the midshaft of each tibiae is subjected to cortical BMD or histology. The femurs are prepared for pqCT scanning of the midshaft prior to biomechanical testing. With respect to lumbar vertebrae (LV), LV2 are processed

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for BMD (pqCT may also be performed); LV3 are prepared for undecalcified bone histology, and LV4 are processed for mechanical testing.

Nature of the Compounds Useful in the Invention

All of the compounds of the invention contain two aromatic systems, Ar¹ and Ar², spaced apart by a linker at a distance of 1.5-15Å, and may preferably contain at least one nitrogen atom. A summary of the structural features of the compounds included within the invention is shown in Figure 1.

As shown, Ar¹ and Ar² may include various preferred embodiments. These are selected from the group consisting of a substituted or unsubstituted aromatic ring system containing a 5-membered heterocycle; a substituted or unsubstituted aromatic ring system containing a six-membered heterocycle; a substituted or unsubstituted naphthalene moiety; and a substituted or unsubstituted benzene moiety. There are 16 possible combinations of these embodiments, if Ar¹ and Ar² are considered distinguishable. As will be clear, however, the designation of one aromatic system as Ar¹ and the other as Ar² is arbitrary; thus there are only ten possible combinations. However, for simplicity, Ar¹ and Ar² are designated separately with the realization that the choice is arbitrarily made. All linkers described herein if not palindromic, are considered to link Ar¹ to Ar² or *vice-versa* whether or not the complementary orientation is explicitly shown (as it is in some cases). Thus, if Ar¹ and Ar² are different and a linker is specified as -CONR-, it is understood that also included is the linker -NRCO- when the designations Ar¹ and Ar² are retained.

The noninterfering substituents on the aromatic system represented by Ar¹ and the noninterfering substituents on the aromatic system represented by Ar² are represented in the formulas herein by R² and R³, respectively. Generally, these substituents can be of wide variety. Among substituents that do not interfere with (and in some instances may be desirable for) the beneficial effect of the compounds of the invention on bone in treated subjects are included alkyl (1-6C, preferably lower alkyl 1-4C), including straight or branched-chain forms thereof, alkenyl (1-6C, preferably 1-4C), alkynyl (1-6C, preferably 1-4C), all of which can be straight or branched chains

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or are aryl (6-10C) or alkylaryl (6-15C) or aryl alkyl (6-15C) and may contain further substituents. R^a and R^b may also include halogens, (e.g. F, Cl, Br and I); siloxy, OR, SR, NR₂, OOCR, COOR, NCOR, NCOOR, and benzoyl, CF₃, OCF₃, SCF₃, N(CF₃)₂. NO, NO₂, CN, SO, SO₂R, SO₃R and the like, wherein R is alkyl (1-6C) or is H. Similarly, these substituents may contain R' as a substitute for R wherein R' is aryl (6-10C) or alkylaryl (6-15C) or aryl alkyl (6-15C). Where R^a or R^b substituents are in adjacent positions in the aromatic system, they may combine to form a ring. Further, rings may be included in substituents which contain sufficient carbon and heteroatoms to provide this possibility.

The choice of noninterfering substituents depends on the overall nature of the system. For example, in compounds of the invention wherein two pyridine rings are linked through a saturated flexible linker, a CF₃ substituent para to the linker in each of the pyridine rings is particularly preferred. In those systems wherein a quinoline is coupled through a flexible conjugated or nonconjugated linker to a phenyl substituent or to a naphthyl substituent, an amino group para to the linker in the phenyl or naphthyl moiety is preferred. Particularly preferred amino groups are dimethylamino and diethylamino. In systems wherein a benzothiazole is coupled to phenyl through a flexible linker, preferred substituents on the phenyl moiety include alkoxy or alkylthio in combination with halo, in particular, chloro. Also preferred is the presence of a diethylamino group in the phenyl moiety para to the position that is coupled to the linker. In general, the presence of a substituent in the phenyl moiety para to the position of joinder to the linker is preferred.

Generally, preferred noninterfering substituents include hydrocarbyl groups of 1-6C, including saturated and unsaturated, linear or branched hydrocarbyl as well as hydrocarbyl groups containing ring systems; halo groups, alkoxy, hydroxy, amino, monoalkyl- and dialkylamino where the alkyl groups are 1-6C, CN, CF₃, OCF₃ and COOR, and the like.

Although the number of R^a and R^b may typically be 0-4 (m) or 0-5 (n) depending on the available positions in the aromatic system, preferred embodiments

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include those wherein the number of R^a is 0, 1 or 2 and of R^b is 0, 1, 2 or 3, particularly 1 or 2.

The linker group, L, may be a covalent bond or any group having a valence of at least two and covering a linear distance of from about 1.5 to about 15 Angstroms, including those that contain cyclic moieties, that meet this spatial requirement. Useful linkers are divided, by definition herein, into three general categories: (1) flexible nonconjugating linkers, (2) flexible conjugating linkers, and (3) constrained linkers. The preferred choice of linker will depend on the choices for Ar¹ and Ar².

As defined herein, flexible nonconjugating linkers are those that link only one position of Ar1 to one position of Ar2, and provide only a single covalent bond or a single chain between Ar1 and Ar2. The chain may contain branches, but may not contain π -bonds (except in the branches) or cyclic portions in the chain. The linker atoms in the chain itself rotate freely around single covalent bonds, and thus the linker has more than two degrees of freedom. Particularly useful flexible nonconjugating linkers, besides a covalent bond, are those of the formulas: -NR-, -CR2-, -S-, or -O-, wherein R is H or alkyl (1-6C), more preferably H or lower alkyl (1-4C) and more preferably H. Also contemplated are those of the formulas: -NRCO-, -CONR-, -CR₂S-, -SCR₂-, -OCR₂-, -CR₂O-, -NRNR-, -CR₂CR₂-, -NRSO₂-, -SO₂NR-, -CR₂CO-, -COCR₂-, and -NR-NR-CO-CR₂- and its complement -CR₂-CO-NR-NR-, or -NRCR2CR2NR- or the thiolated counterparts, and particularly -NHCR2CR2NH-, including the isosteres thereof, such as -NRNRCSNR- and -NRNRCONR-. Also contemplated are those of the formulas: -NH(CH₂)₂NH-, -O(CR₂)₂O-, and -S(CR₂)₂S-, including the isosteres thereof. The optimum choice among flexible nonconjugating linkers is dependent on the nature of Ar¹ and Ar².

Flexible conjugating linkers are those that link only one position of Ar^1 to one position of Ar^2 , but incorporate at least one double or triple bond or one or more cyclic systems in the chain itself and thus have only two degrees of freedom. A flexible conjugating linker may form a completely conjugated π -bond linking system between Ar^1 and Ar^2 , thus providing for co-planarity of Ar^1 and Ar^2 . Examples of useful flexible conjugating linkers include: -RC=CR-; -N=N-; $-C\equiv C-$; -RC=N-; -N=CR-;

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-NR-N=CR-, -NR-NR-CO-CR=CR-, -N=NCOCR₂-, -N=NCSCR₂-, -N=NCOCR₂CR₂, -N=NCONR-, -N=NCSNR-, and the like, where R is H or alkyl (1-6C), preferably H or lower alkyl (1-4C), and more preferably H.

Constrained linkers are those that have more than one point of attachment to either or both Ar¹ and Ar² and, thus, generally allow for only one degree of freedom. Constrained linkers most frequently form fused 5- or 6-membered cyclic moieties with Ar¹ and/or Ar² where either Ar¹ or Ar² has at least one substituent appropriately positioned to form a second covalent bond with the linker, e.g., where Ar² is a phenyl group with a reactive, ortho-positioned substituent, or is derivatized to the linker directly at the ortho position. (Although the aromatic moieties should properly be referred to as phenylene or naphthylene in such cases, generally the term "phenyl" or "naphthyl" is used herein to include both monovalent and bivalent forms of these moieties.) Examples of particularly useful constrained linkers include

and the like, where X is O, N, S or CR, and Y is CR₂ or C=O.

In one class of preferred embodiments, Ar¹ is an aromatic system containing a 5-membered heterocycle, of the formula:

$$R^{a}_{m}$$
 (1a)

or

 R^{a}_{m} (2a)

wherein Z is S, O, NR or -CR₂ in formula (1a) or CR in formula (2a), where each R is independently H or alkyl (1-6C), the dotted line represents an optional π -bond, each R^a is independently a noninterfering substituent as defined above, and m is an integer of 0-4.

In general, Ar² is phenyl, naphthyl, or an aromatic system containing a 5- or 6-membered heterocyclic ring. All may be unsubstituted or substituted with noninterfering substituents, R^b.

When Ar² is an aromatic system containing a six-membered heterocycle, the formula of said system is preferably:

$$\begin{array}{ccc}
R_{p} & z = z \\
z & z & \vdots \\
z - z & \vdots & \vdots
\end{array}$$
(iv)

wherein each Z is independently a heteroatom selected from the group consisting of S, O and N; or is CR or CR₂, the dotted lines represent optional π -bonds, each R^b is independently a noninterfering substituent, and m is an integer of 0-4, with the proviso that at least one Z must be a heteroatom.

Ar² in these compounds may also have the formula

where R^b is a noninterfering substituent as defined above and n is an integer from 0 to 5.

Similarly, when Ar² is naphthyl, it may contain 0-5 R^b substitutions. When Ar² is an aromatic system containing a 5-membered heterocycle, preferred forms are those as described for Ar¹.

Thus, in one set of preferred compounds, Ar1 is

$$R^{a}_{m}$$
 (1a)

or

 R^{a}_{m} (2a)

wherein each R^a is a noninterfering substituent, m is an integer of 0-4, the dotted line represents an optional π bond, and Z is O, S, NR or CR₂ in formula (1) or is CR in formula (2) wherein each R is independently H or alkyl (1-6C).

In one group of these compounds, L is a flexible conjugating or nonconjugating linker. In this group, when Z is NR, Ar² is preferably a substituted or unsubstituted aromatic system containing a 5-membered heterocycle or is

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wherein R^b is a noninterfering substituent and n is an integer of 0-5, and/or L is -N=N-, -N=CR-, -RC=CR-, -NRNR-, -CR₂NR-, -CR₂CR₂-, -NRCO- or -CONR-where R is H or alkyl (1-6C), and/or the dotted line represents a π bond.

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In these embodiments as well as in alternative embodiments of Ar², it is preferred that each R^b is independently halo, OR, SR, NR₂, NO, NO₂, OCF₃ or CF₃ wherein R is H or alkyl (1-6C), or R^b comprises an aromatic system.

Preferred compounds in this group are 59-0100, 59-103, 59-104, 59-105 and 59-106 (See Figure 13).

In another group of these compounds with flexible linkers, Z is S, and Ar² is preferably a substituted or unsubstituted aromatic system containing a 6-membered heterocycle or is of the formula

wherein R^b is a noninterfering substituent and n is an integer of 0-5; and/or L is -N=N-, -N=CR-, -RC=CR-, -NRNR-, -CR₂NR-, -CR₂CR₂-, -NRCO- or -CONR- where R is H or alkyl (1-6C); and/or the dotted line represents a π bond.

In such compounds, regardless of the choice of Ar², preferred are those compounds wherein each R^b is independently halo, OR, SR, NR₂, NO, NO₂, OCF₃ or CF₃ wherein R is H or alkyl (1-6C) or R^b comprises an aromatic system.

Both when Z is S and when Z is NR, it is preferred that m is 0 and/or each R^b is independently OR, SR or halo, where n=2 and at least one R^b is independently OR or SR and/or L is -NHCO- or -CR=CR-.

Preferred compounds in this group include compounds 59-002, 59-0070, 59-0072, 59-0099, 59-0102, the benzothiazole counterpart of 59-0104, 59-0144, 59-0147, 59-0149, 59-0186, 59-0187, 59-0192, 59-0193, 59-0195, 59-0197, 59-0202, 59-0204, 59-0205, 59-0206, 59-0207, 59-0208, and 59-0210, especially the benzothiazole counterpart of 59-0104 or compounds 59-0147, 59-0205 or 59-0210 (See Figure 13)

Z can also be CR, CR₂ or O; here it is also preferred that Ar² is

; and/or

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wherein R^b is a noninterfering substituent and n is an integer of 0-5, and/or L is -N=N-, -N=CR-, -RC=CR-, -NRNR-, -CR₂NR-, -CR₂CR₂-, -NRCO- or -CONR-where R is H or alkyl (1-6C), and/or the dotted line represents a π bond.

In these compounds, too, it is preferred that each R^b is independently halo, OR, SR, NR₂, NO, NO₂, OCF₃ or CF₃ wherein R is H or alkyl (1-6C) or R^b comprises an aromatic system. A preferred compound is 896-5005. (See Figure 4)

The compounds wherein Ar¹ is 1a or 2a as above may also contain a constrained linker.

In these compounds, preferred Z is S or NR; and/or those wherein L is selected from the group consisting of

Ar² is

wherein R^b is a noninterfering substituent and m is 0-4.

Preferably, each R^b is independently halo, OR, SR, NR₂, NO, NO₂, OCF₃ or CF₃ wherein R is H or alkyl (1-6C) or R^b comprises an aromatic system. A preferred compound is 59-0124. (See Figure 13)

In another group of preferred embodiments, Ar¹ is of the formula

$$R^a$$
 (3a)

wherein each R^a is independently a noninterfering substituent or is H and Z is NR, S or O, wherein R is alkyl (1-6C) or H, especially where Z is S and/or wherein Ar^2 is

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wherein R^b is a noninterfering substituent and n is an integer of 0-5,; and/or L is -N=N-, -N=CR-, -RC=CR-, -NRNR-, -CR₂NR-, -CR₂CR₂-, -NRCO- or -CONR-where R is H or alkyl (1-6C), and/or the dotted line represents a π bond. Especially preferred are those compounds where each R^b is independently halo, OR, SR, NR₂, NO, NO₂, OCF₃ or CF₃ wherein R is H or alkyl (1-6C) or R^b comprises an aromatic system.

In another group of compounds, Ar1 is

$$R^a_m$$
 (4a)

wherein R^a is a noninterfering substituent, m is an integer of 0-4, each dotted

line represents an optional π-bond, each Z is independently N, NR, CR or CR₂, where
each R is independently H or alkyl (1-6C) with the proviso that at least one Z is N or
NR.

Particularly preferred members of this group are those wherein Ar1 is

especially those wherein Ar2 is

$$R^{b}_{n}$$
 R^{b}_{m} R^{b}_{m} (vi) or N (via)

wherein each R^b is independently a noninterfering substituent, and n is 0-5 and m is 0-4, and/or L is -N=N-, -RC=CR-, -RC=N-, -NRCO-, -NRCR₂-, -NRCR₂CR₂-, -NRCR₂CO-, -NRNR-, -CR₂CR₂-, -NRCR₂CR₂NR-, -NRCR=CRNR- or -NRCOCR₂NR-.

In general, preferably each R^b is independently halo, OR, SR, NR₂, NO, NO₂, OCF₃ or CF₃ wherein R is H or alkyl (1-6C) or R^b comprises an aromatic system.

In an especially preferred group, m is 0, each R^b is NR₂ or OR and n is 1 or 2, and/or L is -CR=CR-, -N=N- or -NRCO-, especially the compounds of formulas 59-0030, 59-0078, 59-0091, 59-0093, 59-0150, 50-0197, 59-0198, 59-0199 or 59-0480. (See Figure 13)

Also preferred are those wherein Ar¹ has formula (4a) or (5a) and wherein Ar₂ is substituted or unsubstituted quinolyl or naphthyl of the formula

$$R^{b}_{m}$$

$$(viii)$$

$$R^{b}_{m}$$

$$(viii)$$

$$R^{b}_{m}$$

$$R^{b}_{m}$$

$$R^{b}_{m}$$

$$R^{b}_{m}$$

$$R^{b}_{m}$$

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wherein each R^b is a noninterfering substituent and m is 0-4.

Preferred among these are those wherein L is -N=N-, -RC=CR-, -RC=N-,
-NRCO-, -NRCR₂-, -NRCR₂CR₂-, -NRCR₂CO-, -NRNR-, -CR₂CR₂-,
-NRCR₂CR₂NR-, -NRCR=CRNR- or -NRCOCR₂NR-, and/or wherein each R^b is
independently halo, OR, SR, NR₂, NO, NO₂, OCF₃ or CF₃ wherein R is H or alkyl
(1-6C) or R^b comprises an aromatic system and m is 0, 1 or 2.

The compounds 59-0089, 59-0090, 59-0092 or 59-0094 are particularly preferred.

Ar¹ is also preferably

$$R^{a}_{m}$$
 R^{a}_{m} R^{a

wherein each R^a is a noninterfering substituent and m is 0-4, in particular where L is -N=N-, -RC=CR-, -RC=N-, -NRCO-, -NRCR₂-, -NRCR₂CR₂-, -NRCR₂CO-, -NRNR-, -CR₂CR₂-, -NRCR₂CR₂NR-, -NRCR=CRNR- or -NRCOCR₂NR-, and/or Ar² is

wherein R^b is a noninterfering substituent and n is an integer of 0-5. Especially preferred are compounds wherein each R^b is independently halo, OR, SR, NR₂, NO, NO₂, OCF₃ or CF₃ wherein R is H or alkyl (1-6C) or R^b comprises an aromatic system, in particular compounds 59-203, 59-285 or 59-286. (See Figure 13)

When Ar¹ is of formula (4a), L can also be a constrained linker.

In still another preferred set, Ar1 is

wherein each R² is independently a noninterfering substituent, m is an integer of 0-4, each Z is independently N or CR, where R is H or alkyl (1-6C), with the proviso that at least one Z must be N and at least one Z must be CR.

In these compounds, L is preferably a flexible conjugating or nonconjugating linker, and/or wherein Ar² is

$$R^{b}_{n}$$
 (v) or R^{b}_{m} $z=z$ (vi)

wherein each R^b is independently a noninterfering substituent, and in (vi) each Z is independently N or CR, where R is H or alkyl (1-6C), with the proviso that at least one Z must be a N and at least one Z must be CR.

Preferred such compounds have the formula

$$R^{a}_{m}$$
 or R^{b}_{n} R^{b}_{n}

Preferred L embodiments in this group include -N=N-, -RC=CR-, -RC=N-,
-NRCO-, -NRCR₂-, -NRCR₂CR₂-, -NRCR₂CO-, -NRNR-, -CR₂CR₂-,
-NRCR₂CR₂NR-, -NRCR=CRNR- or -NRCOCR₂NR-; preferred for R^a and R^b are
halo, OR, SR, NR₂, NO, NO₂, OCF₃ or CF₃ wherein R is H or alkyl (1-6C) or R^a or R^b
comprise aromatic systems and each m and n is independently 0, 1 or 2.

In particular, compounds are preferred where L is -NHCR₂CR₂NH- and R^a is CF₃ para to L, especially compounds 59-0145, 59-0450, 59-0459 or 59-0483. (See Figure 13)

Finally, in another preferred group, Ar¹ is

wherein each R² is a noninterfering substituent, and n is an integer of 0 and 5, and wherein L is a flexible linker that contains at least one nitrogen. In the alternative or in addition, Ar² is of the formula

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and L is -N=N-, -RC=CR-, -RC=N-, -NRCO-, -NRCR₂-, -NRCR₂CR₂-, -NRCR₂CO-, -NRNRCR₂CR₂-, -NRNRCR=CR-, -NRNRCOCR₂-, -NRNRCOCR₂-, -NRNRCOCR=CR-, -NRNRCSCR=CR-, -NRNRCONR-, -NRNRCSNR-, -NRNR-, -CR₂CR₂-, -NRCR₂CR₂NR-, -NRCR=CRNR- or -NRCOCR₂NR-. It is preferred that each R^b is independently halo, OR, SR, NR₂, NO, NO₂, OCF₃ or CF₃ wherein R is H or alkyl (1-6C) or R^b comprises an aromatic system

Especially preferred are those compounds wherein L is -CR=CRCONRNR-,
-CR=CRCSNRNR-, -CR₂CONRNR- -CR₂CSNRNR-, -NRNRCONR- or
-NRNRCSNR- and/or R^b is -NR₂ and n=1 wherein R^b is in the para position, especially wherein R^a is -COOR and m is 1; most especially compounds 59-0045, 59-0095, 59-0096, 59-0097 and 59-0098. (See Figure 13)

As set forth above, several families of preferred embodiments are defined by specifying Ar^1 and Ar^2 , and L. In one such family, wherein Ar^1 is an aromatic system containing a 5-membered heterocyclic ring, the compound 59-0072, wherein Ar^1 is unsubstituted benzothiazole, the linker $(Ar^1 \rightarrow Ar^2)$ is NHCO, and Ar^2 is 2-methoxy-4-methylthiophenyl was used as a lead compound and variations of the structure studied. Figure 5 shows representative compounds synthesized to analyze the effects of the nature of the linker, various alternatives of Ar^1 wherein Z is O, NR or S, and the effect of substitution on the phenyl moiety, as well as the heterocycle.

Figure 5 gives the structures of these compounds, along with their maximum activity as compared to 59-0008 at 10 μM (the maximum for 59-0008) in the *in vitro* bone growth stimulation assay as well as the concentration at which 50% of maximum stimulation of the BMP promoter was obtained (EC₅₀). See Example 1 for the details of this assay. The results of this study indicate that the amide linker in 59-0072 can readily be substituted by -CH=CH- and that the substitution on the phenyl ring had advantageous effects in the order: 2-Cl-4-OMe=2,4-di-OMe=2-OMe-4-SMe >>3,4-di-OMe=4-OMe. In general, compounds 59-0205, 59-0104, 59-0107, 59-0210 and 59-0124 have the best activity in the primary screen, but only 59-0124 is active in the *ex vivo* calvarial assay described in Example 3.

Similar structure/activity relationship studies were conducted for compounds wherein Ar¹ is quinoline. In this study, compound 50-0197, wherein Ar¹ is unsubstituted quinoline, the linker is -CH=CH-, and Ar² is p-dimethylaminophenyl was used as a lead compound. The compounds synthesized in this study are shown in

5 Figure 6, along with their maximum stimulation characteristics and EC₅₀ in the assay of Example 1. The results of these studies showed that quinoxaline analogs are the most active in the assay, followed by quinoline, the linker can most preferably be -CH=CH- or -N=N- as judged by activity in the assay, but -CH=CH- is preferred *in vivo* due to its lack of toxicity. Preferred substituents on the phenyl ring in Ar² include 2,4-di
10 OMe, 4-NMe₂-2-OMe, and 4-NMe₂. For the compounds in Figure 6, 59-0282 and 50-0197 were moderately active and 59-0203 was highly active in the *ex vivo* calvarial assay described hereinabove as a modification of Gowen, M. and Mundy, G. J.

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Another group of compounds wherein Ar¹ and Ar² are pyridyl heterocycles was also studied. In this case, compound 59-0145 was used as the lead compound; the linker, the nature of the substituents R^a and R^b were varied. In one instance, a quinolyl residue was substituted for a pyrimidine residue as Ar². Representative compounds used in this study are shown in Figure 7, along with the data from the screening assay.

Using 59-0145 as a lead, a CF₃ group in one of Ar¹ and Ar² appeared essential, however, one of R^a or R^b could also be NO₂ or CN. The most preferred linker is -NHCH₂CH₂NH-; substitution on the amino groups in L by an alkyl group appeared to reduce activity. Enhanced chain lengths also led to loss of activity.

Preferred compounds in this group, which perform better than 59-0008 in the screening assay, included 59-0450, 59-0459, 59-0480, and 59-0483.

Finally, a series in which Ar¹ is 3-carboxyphenyl was studied using 59-0045 as the lead compound. In 59-0045, L is -NHN=CH- and Ar² is p-dimethylaminophenyl. Figure 8 shows the compounds synthesized in this series. Under the circumstances of this assay, analogs wherein R^b was, instead of a nitrogen-containing moiety, F, Cl, or OMe were inactive. Preferred compounds in this series are 59-0096 and 59-0098.

30 59-0098 is very active in the ex vivo calvarial assay described above.

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Synthesis of the Compounds Useful in the Invention

Many of the compounds useful in the invention are commercially available and can be synthesized by art-known methods. Those compounds useful in the invention which are new compounds, can similarly be obtained by methods generally known in the art, as described in the Examples below.

The following examples are intended to illustrate, but not to limit, the invention.

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Preparation A

Compound 59-0008 used as a standard in the assays, was synthesized according to the procedure of McDonald, W. S., et al. Chem Comm (1969) 392-393; Irving, H. N. N. H. et al. Anal Chim Acta (1970) 49:261-266. Briefly, 10.0 g of dithizone was taken up in 100 ml EtOH and 50 ml AcOH and heated at reflux for 18 h. After cooling, this was diluted first with 100 ml water and then with 50 ml 1N NaOH. This was then further neutralized by the addition of 6 N NaOH to bring the pH to 5.0. This deep purple mixture was then concentrated on a rotavapor to remove organics. Once the liquid had lost all of its purple color, this was filtered to collect the dark precipitate. Purification by flash chromatography (4.5 x 25.7 cm; EtAc/Hep. (1:4); Rf 0.22) followed by recrystalization from EtOH gave 2.15 g (25% yield) of dark purple crystals, mp=184-185 °C. ¹H NMR (CDCl₃) 7.90 (d of d, J₁=7.7, J₂=2.2, 2H), 7.64 (hump, 1H), 7.49 (m, 3H), 7.02 (m, 1H), 6.91 (m, 2H), 6.55 (d, J=8.1, 1H). MS (EI) 254 (47, M+), 105 (26), 77 [100], 51 (27). HRMS (EI, M+) 254.0626 (calcd 254.0626182). Anal. Calcd for C₁₃H₁₀N₄S: C, 61.40; H, 3.96; N, 22.03. Found: C, 61.40; H, 4.20; N, 22.06.

Example 1

High Throughput Screening

Several tens of thousands of compounds were tested in the assay system set forth in WO 96/38590, published 5 December 1996, and incorporated herein by reference. The standard positive control was 59-0008 (also denoted "OS8"), which is of the formula:

In more detail, the 2T3-BMP-2-LUC cells, a stably transformed osteoblast cell line described in Ghosh-Choudhury *et al. Endocrinology* (1996) 137.331-39, referenced above, was employed. The cells were cultured using α-MEM, 10% FCS with 1% penicillin/streptomycin and 1% glutamine ("plating medium"), and were split 1:5 once per week. For the assay, the cells were resuspended in a plating medium containing 4% FCS, plated in microtiter plates at a concentration of 5 x 10³ cells (in 50 μl)/well, and incubated for 24 hours at 37°C in 5% CO₂. To initiate the assay, 50 μl of the test compound or the control in DMSO was added at 2X concentration to each well, so that the final volume was 100 μl. The final serum concentration was 2% FCS, and the final DMSO concentration was 1%. Compound 59-0008 (10 μM) was used as a positive control.

The treated cells were incubated for 24 hours at 37°C and 5% CO₂. The

20 medium was then removed, and the cells were rinsed three times with PBS. After
removal of excess PBS, 25 µl of 1X cell culture lysing reagent (Promega #E153A) was
added to each well and incubated for at least ten minutes. Optionally, the
plates/samples could be frozen at this point. To each well was added 50 µl of
luciferase substrate (Promega #E152A; 10 ml Promega luciferase assay buffer per 7

25 mg Promega luciferase assay substrate). Luminescence was measured on an

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automated 96-well luminometer, and was expressed as either picograms of luciferase activity per well or as picograms of luciferase activity per microgram of protein.

In this assay, compound 59-0008 (3-phenylazo-1H-4,1,2-benzothiadiazine) exhibited a pattern of reactivity, as shown in Figure 2. The activity for compound 59-0008 was maximal at a concentration of approximately 3-10 µM and, more particularly, at about 3 µM, and thus provided a response of approximately 175 light emission units. Accordingly, other tested compounds were evaluated at various concentrations, and these results were compared to the results obtained for 59-0008 at 10 µM (which value was normalized to 100). For instance, any tested compound in Figure 3 and Figure 4 that showed greater activity than 10 µM of 59-0008 would result in a value over 100.

As shown in Figure 3 (46 sheets) and Figure 4 (28 sheets), several compounds were found to be particularly effective.

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Example 2

In vivo Calvarial Bone Growth Data

Compound 59-0008 was assayed *in vivo* according to the procedure described previously (see "*In vivo* Assay of Effects of Compounds on Murine Calvarial Bone Growth", *supra*). As compared to a vehicle control, compound 59-0008 induced a 4-fold increase in width of new calvarial bone.

In another experiment, 5 week old Swiss white mice were injected 3 times a day for 5 days over the calvaria with compound 59-0203 using PBS, 5% DMSO and 0.1% BSA as carrier. The drug was tested at 6 different doses, from 0.1-50 mg/kg/day. Animals were sacrificed 3 weeks after the injections started and calvariae were fixed, decalcified, and processed for histology. Bone histomorphometry measuring total bone area (BA/TV) confirms that FGF, used in every experiment as a positive control, shows an increase in the total bone area with all doses tested, but this increase is only significantly different from control at 1 and 5 mg/kg/day. The invention compound 59-0203 shows consistent increases over the 0.1-50 mg/kg/day range at a somewhat lower level than that obtained with FGF.

Similar results are obtained when new bone width in microns is measured. There was no new bone present in the control group. 59-0203 caused new bone formation at all doses, with a significant increase at 25-50 mg/kg/day. New bone as percentage of the total bone area was about 45% for the FGF positive control and from about 15% to 30% over the range of 0.1-50 mg/kg/day for 59-0203. There was no new bone present in the negative control.

Example 3

Ex vivo Calvarial Bone Growth Assay

A number of compounds, in particular, those studied in connection with lead compounds classified as hydrazone/hydrazides (H) exemplified by 59-0045, benzothiazoles (T) exemplified by 59-0104, bis-pyridines (P) exemplified by 59-0145, and quinolines/quinoxalines (Q) exemplified by 59-0197, were tested in the *ex vivo* calvarial assay described hereinabove. The results of this assay are shown in Figure 9. In this assay, histomorphotometry and osteoblast numbers are measured and effects are measured on an arbitrary scale from 1-3: i.e., 1, 1+, 2-, 2, 2+, 3-, 3, wherein 1 denotes "inactive." In this assay, for example, FGF scores 2-3.

The scores are assigned to bone formation on the ectocranial periosteal surface.

The area immediately surrounding midline suture is excluded from analysis.

Score

O Toxicity. Cell necrosis, pyknotic nuclei, matrix disintegration.

A score of "1" is the bone forming activity seen in control cultures containing BGJb media + 0.1% bovine serum albumin. The periosteal surface is covered by one layer of osteoblasts (at about 50% of the bone surface, with the remaining 50% being covered by bone lining cells). A score of "1-" is assigned if less than 50% of the periosteal surface is covered by osteoblasts due to inhibitory activity or minor toxicity of the agents being tested. A score of "1+" is given if over 50% of the surface is covered by osteoblasts.

2 A moderate increase in bone forming activity. 20-40% of the periosteal surface is covered by up to two layers of osteoblasts. A score of "2-" is given if less than 20% of the surface is covered by

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two layers and "2+" if more than 40% of the surface is covered by two layers of osteoblasts.

3 A score of "3" is the bone forming activity seen in control cultures containing BGJb media + 0.1% BSA +10% fetal bovine serum. More than 20% of the periosteal surface is covered by three layers of osteoblasts. The cells appear plump (size can exceed 100μm2). A score of "3-" is given if less than 20% of the periosteal surface is covered by three layers of osteoblasts and or osteoblast size is less than 100μm2. A score of "3+" has never been observed.

In all samples, toxicity, ectopic new or woven bone formation associated with osteoblasts, and osteoblast size as reflections of relative activity are noted.

The results shown in Figure 9 represent those obtained when the measurements were made by two different groups. It is clear that a number of compounds tested have activity in this assay. From the results shown in Figure 9, 59-0073, 59-0030, 59-0070, 59-007, 59-0019, 59-0099, 59-0072 and 59-0103 show at least some indication of activity. 59-150 and 59-0104 showed activity when measured by one group but not the other; similarly, 50-0197 had this pattern. It appears that 59-0098 and 59-0203 are quite active in this assay and 59-0145 shows a consistent moderate activity.

Example 4

Stimulation of Bone Growth in Ovariectomized Rats (OVX Assay)

The compound 59-0145 was tested at various concentrations in the OVX assay conducted as described above. The increase in bone volume was measured by two different groups; one group found 5 μg/kg/day of 59-0145 gave 21% increase over control whereas the second group found a 71% increase. At 50 μg/kg/day, the first group found a 31% increase, and the second a 54% increase.

In another experiment, the lumbar vertebrae were measured and the above dosages of 59-0145 were shown to provide a beneficial effect, as shown in Figure 10.

In another experiment, 3 month old Sprague Dawley rats were ovariectomized and depleted for six weeks. At the end of the six weeks, treatment was started with subcutaneous administration of compound 59-0145. The treatment continued for 10

weeks. At the end of the 10 weeks animals were sacrificed, bones were collected for qCT measurements and histology; serum was also collected for osteocalcin determinations.

Figure 11 shows the percentage increase in trabecular bone (proximal tibia) compared to the placebo-treated group in chronic ovariectomized rats after 10 weeks of treatment. Compound 59-0145 causes significant increase in trabecular bone at doses of 50-500 µg/kg/day.

Figure 12 shows results of qCT and bone histomorphometry in proximal tibia in the first two panels, as well as serum osteocalcin levels at the time of sacrifice as a percentage increase compared to control group (OVX placebo-treated group).

Example 5

Chondrogenic Activity

Compounds 59-008, 59-0102 and 50-0197 were assayed for effects on the differentiation of cartilage cells, as compared to the action of recombinant human BMP-2. Briefly, a mouse clonal chondrogenic cell line, TMC-23, was isolated and cloned from costal cartilage of transgenic mice containing the BMP-2 gene control region driving SV-40 large T-antigen, generated as described in Ghosh-Choudhury *et al Endocrinology* 137:331-39, 1996. These cells were cultured in DMEM/10% FCS, and were shown to express T-antigen, and also to produce aggrecan (toluidine blue staining at pH 1.0) and Type-II collagen (immunostaining) by 7 days after confluence.

For measurement of alkaline phosphatase (ALP) activity, the technique of LF Bonewald et al. J Biol Chem (1992) 267:8943-49, was employed. Briefly, TMC-23 cells were plated in 96 well microtiter plates in DMEM containing 10% FCS at 4 x 10³ cells/well. Two days after plating, the cells were confluent and the medium was replaced with fresh medium containing 10% FCS and different concentrations of compounds or recombinant BMP-2. After an additional 2 or 5 days incubation, the plates were washed twice with PBS, and then lysing solution (0.05% Triton X-100) was added (100 µl/well). The cells were lysed by three freeze-thaw cycles of -70°C (30 min), followed by 37°C (30 min with shaking). Twenty microliters of cell lysates

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were assayed with 80 µl of 5 mM p-nitrophenol phosphate in 1.5 M 2-amino-2-methyl-propanol buffer, pH 10.3 (Sigma ALP kit, Sigma Chemical Co., St. Louis, MO) for 10 min at 37°C. The reaction was stopped by the addition of 100 µl of 0.5 M NaOH. The spectrophotometric absorbance at 405 nm was compared to that of p-nitrophenol standards to estimate ALP activity in the samples. The protein content of the cell lysates was determined by the Bio-Rad protein assay kit (Bio-Rad, Hercules, CA). Specific activity was calculated using these two parameters.

At day 2, compounds 59-0008 (10⁻⁹ M), 59-0102 (10⁻⁷ M) and 59-0197 (10⁻⁹ M) increased ALP levels approximately 3-, 2- and 2.5-fold, respectively, as compared to the vehicle control. Recombinant BMP2 at 100, 50 or 10 ng/ml induced ALP levels approximately 10-, 4- or 1.5-fold, respectively, as compared to the vehicle control.

Example 6

Synthesis of Exemplary Compounds

- 15. A. Compounds of the invention wherein Ar¹ is of formula (1a) or (2a) can be synthesized by the procedures described in Dryanska, V. and Ivanov, K. Synthesis (1976) 1:37-8, using the described embodiments of Ar² and the appropriate analogous heterocycle embodied in Ar¹ substituted for the benzothiazole shown. Alternates to the olefin linker described can also be prepared using standard methods.
- Compounds of the invention represented by exemplary Compound 59-0234, wherein Z is O, L is -CH=CH-, and Ar² is 2,4-dimethyoxy-phenyl, including Compounds 59-0211 and 59-0233, were prepared according to the following procedure describing synthesis of Compound 59-0234. Briefly, to a N,N-dimethylformamide (DMF) solution of 2-methylbenzoxazole (1 mmol) and 2,4-dimethoxybenzaldehyde (1 mmol) was added lithium t-butoxide (2 mmol). The reaction mixture was heated at 130°C for 3h. After cooling to room temperature, the reaction mix was poured into ether and washed several times with water. The organic phase was dried over Na₂SO₄, filtered. and evaporated to dryness. The residue was dissolved in a minimal amount of hot ether and, on standing overnight, the crystalline product was collected by filtration.

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B. Exemplary Compound 59-0150 where Ar¹ is of formula 4a was synthesized according to the procedure of Zamboni et al. J Med Chem (1992) 35:3832-44. First, 2-triphenylphosphoniumquinaldine bromide was synthesized as follows. Quinaldine (200 mmols), NBS (200 mmols) and a catalytic amount of benzoyl peroxide (10 mmols) were dissolved in 1 L of anhydrous carbon tetrachloride, and the mixture was stirred under reflux for 72 h. The mixture was cooled to RT and washed with water. The organic layer was drawn off, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to a dark oil. The crude mixture was dissolved in 500 ml of acetonitrile, then triphenylphosphine (200 mmols) was added and the mixture was refluxed under nitrogen overnight. It was then cooled to RT and diluted with anhydrous ether. The precipitated solid was collected by filtration, washed thoroughly with anhydrous ether and dried in vacuo overnight, yielding 25 g of a tan crystalline solid which showed a single spot by TLC (silica gel, 5 % MeOH in DCM).

A Wittig reaction was then performed. Briefly, under anhydrous conditions, 0.738 g (1.68 mmol) 2-triphenylphosphoniumquinaldine bromide in dry THF was cooled to -78°C. 1.0 ml (2.5 mmol, 2.5 M in hexanes) n-butyl lithium was slowly added, and this was allowed to react for 20 min. 0.301 g (1.68 mmol) 4-(N,N-dimethylamino)-2-methoxybenzaldehyde was then added. After a few minutes, the cold bath was removed, and this was left at ambient temp. for 18 h. The reaction was quenched by the addition of aq. sat. NH4Cl. This was extracted with EtAc, and the organics washed with additional NH4Cl, sat. NaHCO3, and sat. NaCl. This was dried over anhydrous Na₂SO₄ and the solvent stripped on a rotavapor. After flash chromatography (3.8 x 18.0 cm; EtAc/Hep. (1:3); Rf 0.29), 0.135 g (26% yield) of a red solid was obtained, mp=185-187 °C. ¹H NMR (CDCl₃) 8.04 (t, J=9.0, 2H), 7.94 (d, J=16.5, 1H), 7.74 (d, J=8.1, 1H), 7.73 (d, J=8.5, 1H), 7.66 (t of d, J_t=7.6, J_d=1.4, 1H), 7.61 (d, J=8.8, 1H), 7.43 (t of d, J_t=7.6, J_d=1.1, 1H), 7.29 (d, J=16.6, 1H), 6.37 (d of d, J₁=8.7, J₂=2.4, 1H), 6.22 (d, J=2.4, 1H), 3.93 (s, 3H), 3.03 (s, 6H). Anal. Calcd for C₂0H₂0N₂O: C, 78.92; H, 6.62; N, 9.20. Found:

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- C. Exemplary Compound 59-0209 was synthesized according to the procedure of McOmie, J. F. W.; and West, D. E., Org Synth, Collect Vol V (1973) 412. Under anhydrous conditions, 0.510 g (1.95 mmol) NNC 59-0198 was slowly treated with 0.38 ml (3.9 mmol) BBr3 in dry CH2Cl2 at -78°C. After 15 min, this was 5 allowed to warm to RT. After 2 h, the reaction was re-cooled to -78°C, and was then quenched by the addition of 1.6 ml (12 mmol) TEA in 25 ml MeOH. After 10 min, this was again allowed to warm to ambient temperature. After 1 h, this was concentrated to dryness on a rotavapor, and twice slurred in MeOH and re-stripped. Purification by flash chromatography (3.0 x 25.6 cm; EtAc/Hep. (1:2); Rf 0.25) gave 10 0.20 g (41% yield) of a slightly yellow solid, mp=271-272 °C (dec.). ¹H NMR (DMSO-d6) 9.77 (s, 1H), 8.31 (d, J=8.6, 1H), 7.96 (d, J=8.6, 1H), 7.92 (d, J=8.3, 1H), 7.82 (d, J=8.6, 1H), 7.74 (d, J=16.6, 1H), 7.72 (t, J=7.6, 1H), 7.58 (d, J=8.6, 2H), 7.53 (t, J=7.6, 1H), 7.26 (d, J=16.5, 1H), 6.83 (d, J=8.6, 2H). Anal. Calcd for C₁₇H₁₃NO: C, 82.57; H, 5.30; N, 5.66. Found:
- D. Exemplary Compound 59-0019 was synthesized as follows: to a xylene solution of 2-methylquinoxaline (10 mmol) and 4-dimethylaminobenzaldehyde (10 mmol) was added piperdine (2 ml). The solution was heated at reflux for 1 day, at which time DBU (200 μL) was added and reflux continued for another 2 days. The solution was cooled to RT and extracted with 1 M citric acid. The aqueous phase was repeatedly extracted with ether. The organic phases were pooled, dried over Na₂SO₄, filtered and evaporated to dryness. The residue was chromatographed on silica gel. The product was eluted using 8:1:1 dicholormethane:ether: hexane. Fractions containing pure product were pooled and evaporated to dryness. The residue was triturated with ether and filtered to give the desired compound.
- E. Exemplary Compound 59-0183 and related Compound 59-0182 were synthesized according to the following procedure. Briefly, quinaldic acid (0.5 mmol) and HATU (0.5 mmol) were dissolved in 2.5 mL of anhydrous DMF in a vial and the solution was stirred at room temperature (RT). Diisopropylethyamine (1 mmol) was added dropwise to the above stirred solution and the mixture was stirred for 15 min.

 The appropriate amine (0.5 mmol) was then added all at once to the above stirred

mixture, and the mixture was stirred overnight at RT. It was then diluted with 25 mL of cold water with vigorous stirring, the precipitate was collected by filtration and washed thoroughly with water several times, and then dried *in vacuo* overnight. The product was purified by flash column chromatography over silica gel eluting with dichloromethane. The pure product was obtained as a tan powder.

- F. Exemplary Compound 59-0209 was synthesized according to the following procedure. Under anhydrous conditions, 0.510 g (1.95 mmol) NNC 59-0198 was slowly treated with 0.38 ml (3.9 mmol) BBr3 in dry CH2Cl2 at -78°C. After 15 min, this was allowed to warm to RT. After 2 h, the reaction was re-cooled to -78°C, and was then quenched by the addition of 1.6 ml (12 mmol) TEA in 25 ml 10 MeOH. After 10 min, this was again allowed to warm to ambient temperature. After 1 h, this was concentrated to dryness on a rotavapor, and twice slurred in MeOH and re-stripped. Purification by flash chromatography (3.0 x 25.6 cm; EtAc/Hep. (1:2); Rf 0.25) gave 0.20 g (41% yield) of a slightly yellow solid, mp=271-272 °C (dec.). ¹H 15 NMR (DMSO-d6) 9.77 (s, 1H), 8.31 (d, J=8.6, 1H), 7.96 (d, J=8.6, 1H), 7.92 (d, J=8.3, 1H), 7.82 (d, J=8.6, 1H), 7.74 (d, J=16.6, 1H), 7.72 (t, J=7.6, 1H), 7.58 (d, J=8.6, 2H), 7.53 (t, J=7.6, 1H), 7.26 (d, J=16.5, 1H), 6.83 (d, J=8.6, 2H). Anal. Calcd for C₁₇H₁₃NO: C, 82.57; H, 5.30; N, 5.66. Found:
- G. Other embodiments wherein AR¹ is of formula (4a) can be synthesized 20 as follows:
 - a. Quinoline azo compounds (59-0030 and 59-0078) may be prepared by reaction of 2-aminoquinoline with a nitrosobenzene (Brown, E. V., et al, J Org Chem (1961) 26:2831-33; Brown, E. V; ______ (1969) 6:571-73).
 - b. Azo derivatives may be obtained by reaction of 2-aminoquinolines with aldehydes, Morimoto, T., et al., Chem Pharm Bull (1977) 25:1607-09; Renault, J., et al., Hebd Seances Acad Sci, Ser C (1975) 280:1041-43; and Lugovkin, B. P.; Zh Obshch Khim (1972) 42:966-69.
 - c. Imino derivatives may be obtained by reaction of 2formylquinolines with anilines, Tran Quoc Son, et al., (1983) 21:22-26; Hagen,

V. et al. Pharmazie (1983) 38:437-39; and Gershuns, A. L., et al., Tr Kom Anal Khim, Akad Nauk SSSR (1969) 17:242-50.

- d. Alternatively conjugated linkers can be formed by bromination of the olefin of 50-0197 with Br₂ in AcOH followed by elimination with DBU as set forth in Zamboni *et al. J Med Chem* (1992) 35:3832-44.
- H. Analogs having the constrained linker depicted below:

may be synthesized by reference to the methods described in Gorbulenko, N.V.

10 et al. Dokl Akad Nauk Ukr SSR (1991) 5:117-23, substituting the 6-membered heterocycle for benzothiazole.

Related, compounds having the constrained linker depicted below:

R= alkyl, OH

may be synthesized by reference to the methods described in the following publications: Chaurasia, M.R. & Sharma, A.J. Acta Cienc Indica Chem (1992) 18:419-22; Kandeel, Maymona M., in Phosphorus, Sulfur, Silicon, Relat Elem (1990) 48:149-55; Salem, M.A. & Soliman, E.A. Egypt J Chem (1985) 27:779-87; Garin, J. et al. Synthesis (1984) 6:520-22, and Ayyangar N. R. et al. Dyes and Pigments (1990) 13:301-10.

I. Exemplary Compound 59-0145 can be synthesized according to the following method. Briefly, a mixture of 2-chloro-5-trifluoromethylpyridine (15 mmol), ethylenediamine (6 mmol), and diisopropylethylamine (18 mmol) was heated at reflux for 18 h. After cooling to room temperature, the solid mass was triturated with

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dichloromethane. The product was filtered and then suspended in hot EtOAc:CHCl₃ (50:50, 800 mL) and filtered to remove insoluble material. The volume was reduced to ~200 mL by heating on a steam bath. On standing, crystals of pure product were deposited.

Related compounds may be synthesized by reference to the method described for Compound 59-0145, and by reference to the methods described in the following publications: Tzikas, A.& Carisch, C., US Patent No. 5,393,306, issued February 28, 1995; Herzig, P.& Andreoli, A., EP 580554, published January 26, 1994; Pohlke, R. & Fischer, W., DE 3938561, published May 23, 1991. Analogs containing the structure O-(CH₂)_n-O may be synthesized by reference to the previous citations, as well as the following publications: Kawato, T. & Newkome, G. Heterocycles (1990) 31:1097-104; Kameko, C. & Momose, Y. Synthesis (1982) 6:465-66; Tomlin, C.D.S. et al., GB 1161492, published August 13, 1969.

- J. Exemplary Compound 59-0097 and exemplary Compound 59-0201 were synthesized according to the following general procedure. Briefly, the isothiocyanate or isocyanate (1 mmol) was dissolved in 5 mL of anhydrous DMF in a vial and the solution was stirred at room temperature (RT). Diisopropylethyamine (2 mmol) was added dropwise to the above stirred solution followed by 3-hydrazinobenzoic acid (1 mmol), and the mixture was stirred overnight at RT. It was then diluted with 50 mL of cold water with vigorous stirring. The precipitate was collected by filtration, washed thoroughly with water several times, and then dried in vacuo overnight. The product was purified by flash column chromatography over silica gel eluting with 5 % methanol in dichloromethane. The pure product was obtained as a red to purple powder. The compounds of the invention are produced by substituting for at least one phenyl group the appropriate heterocycle.
- K. Compounds of the class represented by exemplary Compound 59-0045 can be synthesized using standard procedures for the synthesis of phenyl hydrazones of aromatic aldehydes, as described in any organic textbook. The synthesis of exemplary Compound 59-0045 may be performed as follows. Briefly, a suspension of 3-
- 30 hydrazinobenzoic acid (1 mmol), p-dimethylaminobenzaldehyde (1 mmol), and AcOH

(50 μL) in EtOH:H₂O (4 mL:1 mL) was heated at 105°C in a sealed vial for 3 h. After cooling, a bright yellow solid was removed by filtration. The solid was washed with cold MeOH and then with ether to give pure product.

- L. Exemplary Compound 59-0096 and related, exemplary Compounds 59-0098, 59-0095, 59-0107, 59-0108, 59-0109, 59-0110 and 59-0200 may be synthesized according to the following general procedure. Briefly, the appropriate carboxylic acid (1 mmol) and HATU ([O-(7-azabenzotriazol-1-yl)-1,1,3,3-tritetramethyluronium hexafluorophosphate]; 1 mmol) were dissolved in 5 mL of anhydrous DMF in a vial and the solution was stirred at room temperature (RT). Diisopropylethyamine (3 mmol) was added dropwise to the above stirred solution and the mixture was stirred for 15 min. 3-Hydrazinobenzoic acid (1 mmol) was then added all at once to the above stirred mixture and the mixture was stirred overnight at RT. It was then diluted with 50 mL of cold water with vigorous stirring and the precipitate was collected by filtration and washed thoroughly with water several times and then dried in vacuo overnight. The product was purified by flash column chromatography over silica gel eluting with 5 10 % methanol in dichloromethane. The pure product was obtained as a tan crystalline solid.
- M. Exemplary Compound 59-0097 and exemplary Compound 59-0201 were synthesized according to the following general procedure. Briefly, the

 20 isothiocyanate or isocyanate (1 mmol) was dissolved in 5 mL of anhydrous DMF in a vial and the solution was stirred at room temperature (RT). Diisopropylethyamine (2 mmol) was added dropwise to the above stirred solution followed by 3-hydrazinobenzoic acid (1 mmol), and the mixture was stirred overnight at RT. It was then diluted with 50 mL of cold water with vigorous stirring. The precipitate was

 25 collected by filtration, washed thoroughly with water several times, and then dried in vacuo overnight. The product was purified by flash column chromatography over silica gel eluting with 5 % methanol in dichloromethane. The pure product was obtained as a red to purple powder.
- N. Exemplary Compound 59-0125 where R¹ is methoxy, m is 1, the linker is azo and Ar² is di(2-hydroxyethyl) amino, and related compounds having an azo

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linker can be prepared in a manner similar to that described by Alberti, G. et al. Chim Ind (Milan) (1974) 56:495-97.

O. Exemplary Compound 59-0124 and related, constrained analogs having the structure depicted below:

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may be synthesized by reference to the methods described in Gorbulenko, N.V. et al. Dokl Akad Nauk Ukr SSR (1991) 5:117-23.

Related, constrained analogs having the structure depicted below:

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may be synthesized by reference to the methods described in the following publications: Chaurasia, M.R. & Sharma, A.J. Acta Cienc Indica Chem (1992) 18:419-22; Kandeel, Maymona M., in Phosphorus, Sulfur, Silicon, Relat Elem (1990) 48:149-55; Salem, M.A. & Soliman, E.A. Egypt J Chem (1985) 27:779-87; Garin, J. et al. Synthesis (1984) 6:520-22, or according to the representative procedure described in Ayyangar N. R. et al. Dyes and Pigments (1990) 13:301-10.

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Claims

1. A method to treat a condition in a vertebrate animal characterized by a deficiency in, or need for, bone growth or replacement and/or an undesirable level of bone resorption, which method comprises administering to a vertebrate subject in need of such treatment an effective amount of a compound of the formula:

wherein each of Ar¹ and Ar² is independently a substituted or unsubstituted phenyl, substituted or unsubstituted naphthyl, substituted or unsubstituted aromatic system containing a 6-membered heterocycle or a substituted or unsubstituted aromatic system containing a 5-membered heterocycle; and

L is a linker which spaces Ar¹ from Ar² at a distance of 1.5Å-15Å.

2. The method of claim 1 with the proviso that in the compound of formula (1), if Ar¹ is

and L is

Ar² cannot be

wherein

5 R¹ is selected from the group consisting of:

H, OH, C1-C4 alkyl, C1-C4 alkoxy, C1-C4 alkylthio, halo and (C1-C12)alkyl-carbonyloxy;

R² is selected from the group consisting of:

H, OH, halo, C1-C6 alkyl, C1-C6 alkenyl, C1-C6 alkoxy and (C1-C12)alkyl-carbonyloxy;

R³ is selected from the group consisting of:

H, OH, halo, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 alkenyl and (C1-C12)alkyl-carbonyloxy;

R⁴ is selected from the group consisting of:

H, OH, halo, C1-C6 alkyl, C1-C6 alkoxy and (C1-C12)alkyl-carbonyloxy;

R⁵ is selected from the group consisting of:

H, halo, C1-C6 alkyl, C1-C6 alkoxy, -OC(=O)Me, phthalimide and (C1-C12)alkyl-carbonyloxy;

R⁶ is selected from the group consisting of:

20 H, OH, -NH₂, Cl-C4 alkyl and Cl-C4 alkoxy;

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R⁷ is selected from the group consisting of:

H, C1-C4 alkyl, (C1-C4)alkyl-carbonyl and (C7-C10)arylalkyl;

R⁸ is selected from the group consisting of:

H, OH, haio, -CF₃, C1-C4 haloalkyl, C1-C4 alkyl, C1-C4 alkoxy,

5 -NHC(=O)Me and -N(C1-C4 alkyl)₂;

R⁹ is selected from the group consisting of:

H, OH, halo, -CN, -NO₂, C1-C4 haloalkyl, C1-C8 alkyl, C1-C8 alkoxy, -NHC(=O)Me and -OC(=O)Me;

R¹⁰ is selected from the group consisting of:

H, OH, halo, -CN, -NO₂, C1-C4 haloalkyl, -CO₂H, C1-C12 alkyl, C1-C12 alkoxy, phenyl, C1-C12 alkenyl, (C1-C4)alkoxycarbonyl, -NHC(=O)Me, (C1-C4)alkylcarbonyl, (C1-C12)alkylcarbonyloxy and heteroaryl;

R¹¹ is selected from the group consisting of:

H, OH, halo, C1-C4 haloalkyl, -CF₃, C1-C4 alkyl, -NH₂, C1-C4 alkoxy,

15 -NHC(=O)Me, C1-C4 alkenyl, (C1-C4)alkoxycarbonyl, (C1-C4)alkylcarbonyl, and (C1-C4)alkylcarbonyloxy;

R¹² is selected from the group consisting of:

H, OH, -NH₂, C1-C4 alkyl, C1-C4 alkoxy and (C1-C4)alkylcarbonyl; and R^{13} is selected from the group consisting of:

H, OH, halo, -NH₂, C1-C4 alkyl, C1-C4 alkoxy -N(C1-C4)alkyl.

3. The method of claim 1 with the proviso that in the compound of formula (1), if Ar^1 is

$$R^{a}_{m}$$
 Z Z X Ar^{1}

wherein R^a is a noninterfering substituent; m is an integer of 0-4;

each dotted line represents an optional π -bond;

each Z is independently N, NR, O, S, CR or CR₂, where each R is independently H or alkyl (1-6C);

X is O, S, SO or SO₂; and

L is a flexible linker,

then Ar² is not a substituted or unsubstituted 6-membered aromatic ring; if Ar¹ is

wherein R^a is a noninterfering substituent;

n is an integer of 0 and 5; and

L is a flexible linker which does not contain nitrogen or is a constrained linker, then Ar² is not a substituted or unsubstituted phenyl or a substituted or unsubstituted naphthyl.

4. The method of claim 2 with the further proviso that in the compound of formula (1), if Ar¹ is

$$R^{a}_{m}$$
 X X Ar^{1}

wherein R^a is a noninterfering substituent;

m is an integer of 0-4;

each dotted line represents an optional π -bond;

each Z is independently N, NR, O, S, CR or CR₂, where each R is independently H or alkyl (1-6C);

X is O, S, SO or SO₂; and

L is a flexible linker,

then Ar² is not a substituted or unsubstituted 6-membered aromatic ring;

if Ar1 is

wherein R^a is a noninterfering substituent;

n is an integer of 0 and 5; and

L is a flexible linker which does not contain nitrogen or is a constrained linker, then Ar² is not a substituted or unsubstituted phenyl or a substituted or unsubstituted naphthyl.

5. The method of any of claims 1-4 wherein Ar¹ is

$$R_m^a$$
 (1a)

or

$$R_m^a$$
 (2a)

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wherein each R² is a noninterfering substituent;

m is an integer of 0-4;

the dotted line represents an optional π bond;

Z is O, S, NR or CR₂ in formula (1) or is CR in formula (2) where each R is independently H or alkyl (1-6C); and

L is a flexible conjugating or nonconjugating linker or is a constrained linker.

6. The method of claim 5 wherein L is a flexible conjugating or nonconjugating linker.

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7. The method of claim 6 wherein Z is NR.

8. The method of claim 7 wherein Ar² is a substituted or unsubstituted aromatic system containing a 5-membered heterocycle or is

wherein R^b is a noninterfering substituent and n is an integer of 0-5; and/or
 L is -N=N-, -N=CR-, -RC=CR-, -NRNR-, -CR₂NR-, -CR₂CR₂-, -NRCO- or
 -CONR- where R is H or alkyl (1-6C); and/or
 the dotted line represents a π bond.

- 9. The method of claim 7 wherein each R^b is independently halo, OR, SR, 10 NR₂, NO, NO₂, OCF₃ or CF₃ wherein R is H or alkyl (1-6C) or R^b comprises an aromatic system.
- m is 0, and/or

 each R^b is independently OR, SR or halo;
 where n=2 and at least one R^b is OR or SR; and/or
 L is -NHCO- or -CR=CR-.

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The method of claim 7 wherein

- 11. The method of claim 7 wherein said compound is 59-0100, 59-103, 59-104, 59-105 or 59-106.
 - 12. The method of claim 6 wherein Z is S.
- 13. The method of claim 12 wherein Ar² is a substituted or unsubstituted aromatic system containing a 6-membered heterocycle or is of the formula

wherein R^b is a noninterfering substituent and n is an integer of 0-5; and/or L is -N=N-, -N=CR-, -RC=CR-, -NRNR-, -CR₂NR-, -CR₂CR₂-, -NRCO- or -CONR- where R is H or alkyl (1-6C); and/or

5 the dotted line represents a π bond.

14. The method of claim 13 wherein each R^b is independently halo, OR, SR, NR₂, NO, NO₂, OCF₃ or CF₃ wherein R is H or alkyl (1-6C) or R^b comprises an aromatic system.

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15. The method of claim 13 wherein m is 0; and/or each R^b is independently OR, SR or halo; where n=2 and at least one R^b is OR or SR; and/or L is -NHCO- or -CR=CR-.

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- 16. The method of claim 12 wherein the compound is compound number 59-002, 59-0070, 59-0072, 59-0099, the benzothiazole counterpart of 59-0104, 59-0102, 59-0144, 59-0147, 59-0149, 59-0186, 59-0187, 59-0192, 59-0193, 59-0195, 59-0197, 59-0202, 59-0204, 59-0205, 59-0206, 59-0207, 59-0208, and 59-0210.
- 17. The method of claim 16 wherein the compound is the benzothiazole counterpart of 59-0104, or is compound number 59-0147, 59-0205 or 59-0210.
- 25 18. The method of claim 6 wherein Z is CR or CR₂.
 - 19. The method of claim 18 wherein Ar² is

wherein R^b is a noninterfering substituent and n is an integer of 0-5; and/or L is -N=N-, -N=CR-, -RC=CR-, -NRNR-, -CR₂NR-, -CR₂CR₂-, -NRCO- or -CONR- where R is H or alkyl (1-6C); and/or

- 5 the dotted line represents a π bond.
 - 20. The method of claim 19 wherein each R^b is independently halo, OR, SR, NR₂, NO, NO₂, OCF₃ or CF₃ wherein R is H or alkyl (1-6C) or R^b comprises an aromatic system.
 - 21. The method of claim 6 wherein Z is O.
 - 22. The method of claim 21 wherein Ar² is of the formula

$$\mathbb{R}^{b}_{n}$$
 (v)

- wherein R^b is a noninterfering substituent and n is an integer of 0-5, and/or
 L is -N=N-, -N=CR-, -RC=CR-, -NRNR-, -CR₂NR-, -CR₂CR₂-, -NRCO- or
 -CONR- where R is H or alkyl (1-6C); and/or
 the dotted line represents a π bond.
- 23. The method of claim 19 wherein each R^b is independently halo, OR, SR, NR₂, NO, NO₂, OCF₃ or CF₃ wherein R is H or alkyl (1-6C) or R^b comprises an aromatic system.
- The method of claim 21 wherein the compound of formula (1) is compound number 896-5005.

10

; and/or

- 25. The method of claim 5 wherein L is a constrained linker.
- 26. The method of claim 25 wherein Z is S or NR; and/or wherein L is selected from the group consisting of

wherein Ar² is

wherein R^b is a noninterfering substituent and m is 0-4.

- 27. The method of claim 25 wherein each R^b is independently halo, OR, SR, NR₂, NO, NO₂, OCF₃ or CF₃ wherein R is H or alkyl (1-6C) or comprises an aromatic system.
- The method of claim 25 wherein the compound of formula (1) is 59-0124.
 - 29. The method of any of claims 1-4 wherein Ar¹ is of the formula

$$R^a$$
 (3a)

wherein each R² is independently a noninterfering substituent or is H; and Z is NR, S or O, wherein R is alkyl (1-6C) or H.

30. The method of claim 29 wherein Z is S; and/or wherein Ar² is

wherein R^b is a noninterfering substituent and n is an integer of 0-5; and/or L is -N=N-, -N=CR-, -RC=CR-, -NRNR-, -CR₂NR-, -CR₂CR₂-, -NRCO- or -CONR- where R is H or alkyl (1-6C); and/or

the dotted line represents a π bond; and/or
each R^b is independently halo, OR, SR, NR₂, NO, NO₂, OCF₃ or CF₃ wherein
R is H or alkyl (1-6C) or comprises an aromatic system.

31. The method of any of claims 1-4 wherein Ar¹ is

$$R^a_m$$
 (4a)

wherein R^a is a noninterfering substituent;

m is an integer of 0-4;

each dotted line represents an optional π -bond;

each Z is independently N, NR, CR or CR₂, where each R is independently H or alkyl (1-6C) with the proviso that at least one Z is N or NR.

20 32. The method of claim 31 wherein Ar¹ is

$$R^a_m$$
 (5a)

33. The method of claim 31 wherein Ar₂ is

$$R^{b}_{n}$$
 R^{b}_{m} R^{b}_{m} (vi) or N (via)

wherein each R^b is independently a noninterfering substituent, and n is 0-5 and m is 0-4; and/or

- L is -N=N-, -RC=CR-, -RC=N-, -NRCO-, -NRCR₂-, -NRCR₂CR₂-, -NRCR₂CO-, -NRNR-, -CR₂CR₂-, -NRCR₂CR₂NR-, -NRCR=CRNR- or -NRCOCR₂NR-.
- 34. The method of claim 33 wherein each R^b is independently halo, OR, SR, NR₂, NO, NO₂, OCF₃ or CF₃ wherein R is H or alkyl (1-6C) or R^b comprises an aromatic system.
- The method of claim 32 wherein
 each R^b is NR₂ or OR and m and n are 0, 1 or 2; and/or
 L is -CR=CR-,-N=N- or -NRCO-.
 - 36. The method of claim 35 wherein the compound of formula (1) is 59-0030, 59-0078, 59-0091, 59-0093, 59-0150, 50-0197, 59-0198, 59-0199 or 59-0480.

37. The method of claim 31 wherein Ar₂ is substituted or unsubstituted quinolyl or naphthyl of the formula

$$R^{b}_{m}$$

$$(viii)$$

$$R^{b}_{m}$$

$$(viii)$$

$$R^{b}_{m}$$

$$R^{b}_{m}$$

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wherein each R^b is a noninterfering substituent and m is 0-4.

- 38. The method of claim 37 wherein L is -N=N-, -RC=CR-, -RC=N-,
 -NRCO-, -NRCR₂-, -NRCR₂CR₂-, -NRCR₂CO-, -NRNR-, -CR₂CR₂-,
 -NRCR₂CR₂NR-, -NRCR=CRNR- or -NRCOCR₂NR-; and/or
 wherein each R^b is independently halo, OR, SR, NR₂, NO, NO₂, OCF₃ or CF₃ wherein R is H or alkyl (1-6C) or R^b comprises an aromatic system and m is 0, 1 or 2.
- 10 39. The method of claim 38 wherein the compound of formula (1) is 59-0089, 59-0090, 59-0092 or 59-0094.
 - 40. The method of claim 31 wherein Ar¹ is

$$R^{a}_{m}$$
 (6a) or N (7a) or N (8a)

wherein each R^a is a noninterfering substituent and m is 0-4.

41. The method of claim 40 wherein L is -N=N-, -RC=CR-, -RC=N-, -NRCO-, -NRCR₂-, -NRCR₂CR₂-, -NRCR₂CO-, -NRNR-, -CR₂CR₂-, -NRCR₂CR₂-, -NRCR₂CR₂NR-, -NRCR=CRNR- or -NRCOCR₂NR-; and/or Ar² is

wherein R^b is a noninterfering substituent and n is an integer of 0-5; and/or wherein each R^b is independently halo, OR, SR, NR₂, NO, NO₂, OCF₃ or CF₃ wherein R is H or alkyl (1-6C) or R^b comprises an aromatic system.

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- 42. The method of claim 41 wherein the compound of formula (1) is 59-203, 59-285 or 59-286.
 - 43. The method of claim 31 wherein L is a constrained linker.

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44. The method of any of claims 1-4 wherein Ar¹ is

$$\begin{array}{cccc}
R^{a}_{m} & z = z \\
\hline
z & & \\
z - z
\end{array}$$
(9a)

wherein each R^a is independently a noninterfering substituent; m is an integer of 0-4;

15

- each Z is independently N or CR, where R is H or alkyl (1-6C), with the proviso that at least one Z must be N and at least one Z must be CR.
- 45. The method of claim 44 wherein L is a flexible conjugating or nonconjugating linker; and/or
- wherein Ar² is

$$R^{b}_{n}$$
 (v) or Z_{z-z} (vi)

wherein each R^b is independently a noninterfering substituent, and

in (vi) each Z is independently N or CR, where R is H or alkyl (1-6C), with the proviso that at least one Z must be a N and at least one Z must be CR.

46. The method of claim 45 wherein the compound of formula (1) is of the formula

$$R^{a}_{m}$$
 or R^{b}_{n}

- The method of claim 46 wherein L is -N=N-, -RC=CR-, -RC=N-, -NRCO-, -NRCR₂-, -NRCR₂CR₂-, -NRCR₂CO-, -NRNR-, -CR₂CR₂-,
- -NRCR₂CR₂NR-, -NRCR=CRNR- or -NRCOCR₂NR-, and/or
 wherein each R² and R^b is independently halo, OR, SR, NR₂, NO, NO₂, OCF₃
 or CF₃ wherein R is H or alkyl (1-6C) or R^b comprises an aromatic system and each m
 and n is independently 0, 1 or 2.
- The method of claim 47 wherein L is -NHCR₂CR₂NH-, m is 1 and R² is CF₃ para to L.
 - 49. The method of claim 48 wherein the compound of formula (1) is 59-0145, 59-0450, 59-0459 or 59-0483.
 - 50. The method of any of claims 1-4 wherein Ar¹ is

wherein each R^a is a noninterfering substituent, and n is an integer of 0 and 5, and

wherein L is a flexible linker that contains at least one nitrogen; and/or

wherein Ar² is of the formula

and L is -N=N-, -RC=CR-, -RC=N-, -NRCO-, -NRCR₂-, -NRCR₂CR₂-, -NRCR₂CO-, -NRNRCR₂CR₂-, -NRNRCR=CR-, -NRNRCOCR₂-, -NRNRCOCR=CR-, -NRNRCSCR=CR-, -NRNRCONR-, -NRNRCSNR-, -NRNR-, -CR₂CR₂-, -NRCR₂CR₂NR-, -NRCR=CRNR- or -NRCOCR₂NR-.

- 51. The method of claim 50 wherein each R^b is independently halo, OR, SR, NR₂, NO, NO₂, OCF₃ or CF₃ wherein R is H or alkyl (1-6C) or R^b comprises an aromatic system.
- 52. The method of claim 50 wherein L is -CR=CRCONRNR-,
 -CR=CRCSNRNR-, -CR₂CONRNR- -CR₂CSNRNR-, -NRNRCONR- or
 -NRNRCSNR- and/or
 R^b is -NR₂ and n=1 wherein R^b is in the para position.
 - 53. The method of claim 50 wherein R^a is -COOR and m is 1.
- 20 54. The method of claim 52 wherein the compound of formula (1) is 59-0045, 59-0095, 59-0096, 59-0097 or 59-0098.
- 55. A pharmaceutical composition for use in a method to treat a condition in a vertebrate animal characterized by a deficiency in, or need for, bone growth
 replacement and/or an undesirable level of bone resorption which composition contains a pharmaceutically acceptable excipient and an effective amount of a compound of the formula set forth in any preceding claim.

56. A compound for use in preparing a composition for use in the treatment of a condition in a vertebrate animal characterized by a deficiency in, or need for, bone growth replacement and/or an undesirable level of bone resorption which method comprises administering said composition to a vertebrate subject, said compound set forth in any preceding claim.

Ar ¹ – linker 1.5 – 15	(1)	
Ar ¹	Ar ²	
contains 5-membered heterocycle	substituted or unsubsituted benzene	II-A
contains 5-membered heterocycle	substituted or unsubstituted naphthalene	II-8
contains 5-membered heterocycle	contains 6-membered heterocycle	II-C
contains 5-membered heterocycle	contains 5-membered heterocycle	II-D
contains 6-membered heterocycle	substituted or unsubstituted benzene	II-E
contains 6-membered heterocycle	substituted or unsubstituted naphthalene	II-F
contains 6-membered heterocycle	contains 6-membered heterocycle	II-G
substituted or unsubstituted naphthalene	substituted or unsubstituted benzene	ІІ-н
substituted or unsubstituted naphthalene	substituted or unsubstituted naphthalene	II–I
substituted or unsubstituted benzene	substituted or unsubstituted benzene	II-J

FIG. I

	CELLS		10/1/96				· · · · · · · · · · · · · · · · · · ·
5x 103 CE	LLS/WELL	_					
	, uM	READ 1	READ 2	AVERAGE	INDUCTION	AVE-BASAL	%MAX
0S-8	100.000	0.21	0.22	0.22	0.18	-0.99	-17.90
	31.250	3.96	4.44	4.20	3.49	3.00	54.26
	9.766	6.99	6.46	6.72	5.59	5.52	100.00
	3.052	4.62	4.88	4.75	3.95	3.55	64,22
	0.954	3.13	3.16	3.14	2.61	1.94	35.12
	0.298	2.75	2.59	2.67	2.22	1.47	26.58
	0.093	2.10	2.04	2.07	1.72	0.87	15.77
	0.029	1.56	1.71	1.63	1.36	0.43	7.60
	0.0091	1.45	1.42	1.44	1.19	0.23	4.21
	0.0028	1.28	1.37	1.33	1.10	0.12	2.25
	0.0000	1.32	1.30	1.31			٠
		AVERAGE BA		1.20		· · · · · · · · · · · · · · · · · · ·	
100.0 80.0 60.0 № 40.0 20.0	00 +	0.01	0.10	DOSE RESPO		0.00	OS-8

FIG. 2

SUBSTITUTE SHEET (RULE 20)

NNC#	MOL.WEIGHT	CONCENTR	MOTTA	%RESPONSE	
· ·	WOL.WEIGHT	CONCENTR	AHON	MESFUNSE	
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1	1				
		:			
50-0194	430.33	- 100 00			
50-0194		100.00		-19.190	
***	1	31.25		32.450	· · · · · · · · · · · · · · · · · · ·
	 	9.77 t 3.05 t		-14.240 -11.330	
	 	953.67 ir		-12. 79 0	
		298.02 r		-13.450	
		93.13		- 12.290	
		29.10		-9.440	
		9.09		-6.450	
		2.84	nΜ	-8.130	
		888.18		-3.320	
		\exists			
]			Ì	
50-0195	275.36				
50-0195		100.00 և		-4.630	
		31.25 u		16.790	
		9.77 L		62.830	
		3.05 L		102.720	
		953.67 r		60.860	·
		298.02 r		32.450	
		93.13 r		19.340	
	 	29.10 r		17.220	
		9.09 r 2.84 r	nM NA	5.640	
	 	888.18	M -	4.840 5.640	
		000.10	<u> </u>	3.070	
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Ĭ.+					
0/140	1	İ			
50-0196	276.30				
50-0196		100.00	JM.	-16.210	
	-	31.25 L	ıM	-8.560	
		9.77 (11.620	
	 	3.05 t		27.790	
	 	953.67 r		18.390	
		298.02 r		6.230	
	 	93.13 r 29.10 r		12.420	
· · · · · · · · · · · · · · · · · · ·	 i	29.10 r 9.09 r		12.630 6.590	
	 	2.84 r	ım nM	7.970	
· · · · · · · · · · · · · · · · · · ·	1	888.18	M	5.060	
		000.10		0.000	

FIG. 3 SUBSTITUTE SHEET (RULE 26)

NNC#	MOL.WEIGHT	CONCENT	RATION	%RESPONSE	
1					
50.0101					
50-0194 50-0194	430.33	100.00		10.100	
130-0194		100.00 31.25		-19.190	
		9.77		32.450 -14.240	
		3.05		-11.330	
		953.67		-12.790	
		298.02	nΜ	-13,450	
		93.13		-12.290	
		29.10		-9.440	· · · · · · · · · · · · · · · · · · ·
		9.09 2.84		<u>-6.450</u>	
		888.18		-8.130 -3.320	
		000.10	,,,,	-3.320	
IN I M			i I		
50-0195	275.36				
50-0195		100.00		-4.630	
		31.25		16.790	
		9.77		62.830	
		3.05		102.720	
		953.67 298.02		60.860	
		93.13		32.450 19.340	
		29.10		17.220	
		9.09		5.640	
		2.84	nM	4.840	
		888.18	рМ	5.640	
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N' N'	İ				
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0/10]]	
E0 0400					
50-0196 50-0196	276.30	100.00		1000	
00 0130		100.00 31.25		-16.210	
	 	9.77		-8.560 11.620	
		3.05		27.790	
		953.67		18.390	
		298.02	nM	6.230	
		93.13	nM	12,420	
		29.10	nM	12.630	
		9.09	nM	6.590	
		2.84 888.18	nM nM	7.970 5.060	
		000.10	hu.	1 3.000	

FIG. 3A SUBSTITUTE SHEET (RULE 26)

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A A				1	
N			İ		
1					
50-0197	274.37				
50-0197		100.00	υM	-18.250	
		31.25	uM	-14.980	
		9.77		4.040	-
		3.05		93.790	
		953.67		205,530	
		298.02	InM	242,920	
<u> </u>		93.13		195.890	
	 	29.10		115.320	
		9.09	InM	85.630	
	 	2.84 888.18		54.380 33.180	~
Н	1	500.10	DIN:	33.160	
N _N]]			}	
			[
3 4]		
59-0008	054.70				
39-0008	254.32	-			
				1	
" []					-
\ \frac{1}{2}					
59-0019	59-0019	100.00			
59-0019		100.00		-22.240	
		31.25 9.77		-22.670	
		3.05		-17.470 74.490	
		<u>5.05</u> 953.67			
		298.02		198.080 258.340	
		93.13		225.350	
		29.10		75.220	
		9.09	nM	24.030	
		2.84	lnM	34.480	
		888.18	рМ	-3.740	
		<u> </u>			
CI					
59-0020	266.73				
150 0000		100.00		-16.510	
59-0020	 				
59-0020		31.25	uM	-16.040	
159-0020		9.77	luM	-0.270	
159-0020		9.77 3.05	uM uM	-0.270 96.490	
159-0020		9.77 3.05 953.67	uM uM nM	-0.270 96.490 153.320	
159-0020		9.77 3.05	luM luM lnM lnM	-0.270 96.490	

FIG. 3B SUBSTITUTE SHEET (RULE 28)

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29.10 nM	37.870
9.09 nM	24.820
2.84 nM	20.500
888.18 pM	13.310

FIG. 3C

				·	
Ci Ci					
l " 」	1				
59-0021	284.72				
59-0021		100.00	uМ	-16.310	
		31.25		-12.850	
		9.77		84.130	
		3.05		89.940	
		953.67		65,750	
		298.02		33.940	
		93.13		22.560	
		29.10		25.020	
		9.09 2.84		13.910	
		888.18	InM	33.270 15.500	
			TIPIN	13.300	
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59-0022	266,37				
59-0022		100.00		7.250	
		31.25		-2.070	
		9.77		-0.270	
		3.05		4.390	
		953.67		3.060	
		298.02		-1.800	
		93.13		-0.200	
		29.10		-3.270	
		9.09 2.84	nM nM	1.130	
		888.18	nM	2.590 2.460	
		000.10	P 101	2.400	
OH _O					
N. N.					
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50,0007					
<u>59-0023</u> 59-0023	239.28				
33-0023		100.00		-12.720	
· · · · · · · · · · · · · · · · · · ·		31.25		33.140	
		9.77		56.500	
-		3.05		29.550	
		953.67		25.360	
		298.02 93.13	nM nM	15.700	
		29.10		7.380	
		9.09		9.710	
		2.84	nM	1.000 4.520	
		888.18		-0.010	
				0.010	

FIG. 3D Substitute sheet (Rule 20)

	,				
59-0024 59-0024	220.28				
Ϊ]				
59-0025	224.31				
59-0025		100.00		-25.590	
		31.25		14.150	
		9.77		50.690	
		3.05		57.880	
		953.67		38.900	
		298.02	nМ	28.530	
		93.13		19.660	
		29.10	nM	17.490	
		9.09	'nМ	-0.600	
		2.84	nM	-4.190	
		888.18	рМ	4.670	
			·		
50 0026	040 00				
59-0026 59-0026	248.29	100.00	uM	-29.830	
03-0020		31.25	··M	-29.630 -9.440	
		9.77		-10.470	
<u> </u>	 - 	3.05		46.220	
-				107.760	
		953.67 298.02	nM	86.720	
	 	93.13		36.850	
				26.720	
	 	29.10		8.520	
	 	9.09		-1.240	
	 	2.84 888.18			
	11	000,10	lhw	4.020	

FIG. 3E

SUBSTITUTE SKEET (RULE 20)

					
H H					
59-0027	250.30			ł	
59-0027		100.00	uM	89.810	
		31.25	uМ	54.670	· · · · · · · · · · · · · · · · · · ·
		9.77	uM	44.940	
		3.05	uM	23.780	
		953.67		8.380	
		298.02	nM	6.330	·
		93.13	nM	7.360	
		29.10	nM	3.380	
		9.09		-1.620	
		2.84	nΜ	-3.670	
		888.18	рМ	-0.720	
59-0028	226.28		·		
59-0028		100.00	пM	-26.750	
		31.25		-16.740	
	 	9.77		29.550	
	-	3.05		100.580	
	 	953.67		54.940	
		298.02		31.340	
		93.13	nM	7.500	
		29.10		7.500	
		9.09		7.880	
	· .	2.84		3.140	
		888.18		4.670	

FIG. 3F

SUBSTITUTE SHEET (RULE 20)

				1	
			[i
59-0029	249.27				
59-0029		100.00		-15.160	
		31.25		41.940	
		9.77		36.630	
		3.05		7.120	
		953.67		21.880	
		298.02		15.540	_
	<u>.</u>	93.13		1.810	
		29.10		1.370	
		9.09		12.140	
		2.84		-4.230	
	<u>_</u>	888.18	PΜ	9.040	
N N N					
			•		İ
59-0030A	233.28				
59-0030A	~~~~	100.00	иM	-27.970	
		31.25	uM	-22.830	
		9.77		-5.420	
		3.05	υM	57.280	
		953.67	nM	72.620	
		298.02	nM	53.000	
		93.13	nM	29.990	
		29.10	nM	14.630	
		9.09	nM	3.870	
		2.84		6.970	
		888.18	рМ	1.810	
				•	
]		
59-0031	231.30				
59-0031		100.00		-25.790	
		31.25		-17.810	
		9.77	uM	20.840	
		3.05		87.380	
		953.67		49.320	
		298.02		43.110	
		93.13		29.530	
		29.10		1.810	
		9.09	lnM	1.220	
		2.84		-0.550	
	<u> </u>	888.18	JPM	4.160	

FIG. 3G SUBSTITUTE SHEET (RULE 20)

59-0032 59-0032 100.00 uM		 			T	т
S9-0032 248.29 100.00 UM		1			1	
S9-0032 248.29 100.00 UM						
S9-0032 248.29 100.00 UM					1	į
100.00 uM	· • • • • • • • • • • • • • • • • • • •]
31.25 UM 40.750 9.77 UM 42.820 3.05 UM 25.700 9.53.67 nM 31.170 298.02 nM 34.410 9.31.31 nM 3.570 29.10 nM 4.320 9.09 nM -10.000 2.284 nM 5.650 888.18 pM 11.990 59-0033 248.29 59-0033 100.00 UM -28.180 9.77 UM 55.300 3.05 UM 49.710 953.67 nM 47.410 298.02 nM 0.250 9.313 nM 7.980 298.02 nM 0.250 93.13 nM 7.980 29.10 nM -8.940 9.09 nM -7.630 28.84 nM -0.400 888.18 pM -5.980		248.29	100.00	ļ.,.		
9.77 luM 42.820 3.05 luM 25.700 953.67 lnM 31.170 298.02 lnM 34.410 93.13 lnM 3.570 29.10 lnM 4.320 9.09 lnM -10.000 2.84 lnM 5.650 888.18 lpM 11.990 59-0033 100.00 luM -28.180 9.77 luM 55.300 3.05 luM 49.710 953.67 lnM 47.410 993.13 lnM 7.980 9.09 lnM -2.800 9.09 lnM -2.800 9.09 lnM -2.800 9.09 lnM -2.800 9.09 lnM -2.800 9.09 lnM -2.800 9.09 lnM -2.800 9.09 lnM -2.800 9.09 lnM -2.800 9.09 lnM -2.800 9.09 lnM -2.800 9.09 lnM -2.800 9.09 lnM -3.580	35-0032	├ ─── ─				<u> </u>
3.05 luM 25.700 953.67 lnM 31.170 298.02 lnM 34.410 93.13 lnM 3.570 29.10 lnM 4.320 9.09 lnM -10.000 2.84 lnM 5.650 888.18 lpM 11.990 59-0033 100.00 luM -28.180 31.25 luM -11.590 9.77 luM 55.300 3.05 luM 49.710 953.67 lnM 47.410 298.02 lnM 0.250 93.13 lnM 7.980 29.10 lnM -8.940 9.09 lnM -7.630 2.84 lnM -0.400 888.18 lpM -5.980 31.25 luM -28.51 953.67 lnM 47.358 3.05 luM 37.91 953.67 lnM 37.91 953.67 lnM 37.91 953.67 lnM 20.09 298.02 lnM 20.09						<u> </u>
953.67 nM 31.170		 				
298.02 nM 34.410 93.13 nM 3.570 29.10 nM 4.320 9.09 nM -10.000 2.84 nM 5.650 888.18 pM 11.990		 				
93.13 nM 3.570 29.10 nM 4.320 9.09 nM -10.000 2.84 nM 5.650 888.18 pM 11.990 59-0033 100.00 uM -28.180 9.77 uM 55.300 9.77 uM 55.300 9.77 uM 55.300 9.77 uM 47.410 9.77 uM 7.980 9.77 uM -7.630 9.99 nM -7.630						
29.10 nM		 	290.02	nm -M		ļ
9.09 nM -10.000 2.84 nM 5.650 888.18 pM 11.990 59-0033 100.00 uM -28.180 31.25 uM -11.590 9.77 uM 55.300 3.05 uM 49.710 953.67 nM 47.410 298.02 nM 0.250 93.13 nM 7.980 29.10 nM -8.940 9.09 nM -7.630 2.84 nM -0.400 888.18 pM -5.980 59-0034 268.34 59-0034 100.00 uM -28.51 31.25 uM 24 9.77 uM 73.58 3.05 uM 37.91 953.67 nM 37.91 953.67 nM 20.09		<u> </u>				
2.84 nM 5.650 888.18 pM 11.990 59-0033 248.29 59-0033 100.00 uM -28.180 31.25 uM -11.590 9.77 uM 55.300 3.05 uM 49.710 953.67 nM 47.410 298.02 nM 0.250 93.13 nM 7.980 29.10 nM -8.940 9.09 nM -7.630 28.4 nM -0.400 888.18 pM -5.980 59-0034 268.34 100.00 uM -28.51 31.25 uM 24 9.77 uM 373.58 31.25 uM 24 9.77 uM 373.58 31.25 uM 73.58 31.25 uM 73.58 31.25 uM 73.58						
59-0033 248.29 59-0033 248.29 100.00 uM		<u> </u>	9.09	INM		
59-0033 248.29 100.00 tuM			2.04	nM nV		
100.00 uM		 	000.18	i i	11.990	
100.00 uM]	
100.00 uM				•		
100.00 uM	~ W X Y	1	į			
100.00 uM					ļ	
31.25 uM -11.590 9.77 uM 55.300 3.05 uM 49.710 953.67 nM 47.410 298.02 nM 0.250 93.13 nM 7.980 29.10 nM -8.940 9.09 nM -7.630 2.84 nM -0.400 888.18 pM -5.980 59-0034 268.34 59-0034 268.34 100.00 uM -28.51 31.25 uM 24 9.77 uM 73.58 3.05 uM 37.91 953.67 nM 20.09 298.02 nM 20.09	59-0033	248.29			ł I	
31.25 uM -11.590 9:77 uM 55.300 3.05 uM 49.710 953.67 nM 47.410 298.02 nM 0.250 93.13 nM 7.980 29.10 nM -8.940 9.09 nM -7.630 2.84 nM -0.400 888.18 pM -5.980 59-0034 268.34 100.00 uM -28.51 31.25 uM 24 9.77 uM 73.58 3.05 uM 37.91 953.67 nM 20.09 298.02 nM 16.87	59-0033		100.00	uМ	-28.180	-
9:77 uM 55.300 3.05 uM 49.710 953.67 nM 47.410 298.02 nM 0.250 93.13 nM 7.980 29.10 nM -8.940 9.09 nM -7.630 2.84 nM -0.400 888.18 pM -5.980 59-0034 100.00 uM -28.51 31.25 uM 24 9.77 uM 73.58 3.05 uM 37.91 953.67 nM 20.09 298.02 nM 16.87			31.25	uМ		
953.67 nM 47.410 298.02 nM 0.250 93.13 nM 7.980 29.10 nM -8.940 9.09 nM -7.630 2.84 nM -0.400 888.18 pM -5.980 59-0034 100.00 uM -28.51 31.25 uM 24 9.77 uM 73.58 3.05 uM 37.91 953.67 nM 20.09 298.02 nM 16.87			9:77	uM	55.300	
953.67 nM 47.410 298.02 nM 0.250 93.13 nM 7.980 29.10 nM -8.940 9.09 nM -7.630 2.84 nM -0.400 888.18 pM -5.980 59-0034 100.00 uM -28.51 31.25 uM 24 9.77 uM 73.58 3.05 uM 37.91 953.67 nM 20.09 298.02 nM 16.87			3.05	uМ	49.710	
93.13 nM 7.980 29.10 nM -8.940 9.09 nM -7.630 2.84 nM -0.400 888.18 pM -5.980 59-0034 59-0034 100.00 uM -28.51 31.25 uM 24 9.77 uM 73.58 3.05 uM 37.91 953.67 nM 20.09 298.02 nM 16.87			953.67	nM	47.410	
29.10 nM -8.940 9.09 nM -7.630 2.84 nM -0.400 888.18 pM -5.980 59-0034 100.00 uM -28.51 31.25 uM 24 9.77 uM 73.58 3.05 uM 37.91 953.67 nM 20.09 298.02 nM 16.87			298.02	nM	0.250	1
9.09 nM -7.630 2.84 nM -0.400 888.18 pM -5.980 59-0034 268.34 59-0034 100.00 uM -28.51 31.25 uM 24 9.77 uM 73.58 9.77 uM 37.91 953.67 nM 20.09 298.02 nM 16.87			93.13	nM	7.980	
9.09 nM -7.630 2.84 nM -0.400 888.18 pM -5.980 59-0034 268.34 59-0034 100.00 uM -28.51 31.25 uM 24 9.77 uM 73.58 9.77 uM 37.91 953.67 nM 20.09 298.02 nM 16.87			29.10	nM	-8.940	
2.84 nM			9.09	nM		_
S88.18 pM -5.980			2.84	nM	-0.400	
59-0034 59-0034 100.00 uM -28.51 31.25 uM 24 9.77 uM 73.58 3.05 uM 37.91 953.67 nM 20.09 298.02 nM 16.87			888.18	рМ		
100.00 uM						
100.00 uM					1	i
100.00 uM						
100.00 uM	N N N N	1				
100.00 uM			- 1			i
31.25 uM 24 9.77 uM 73.58 3.05 uM 37.91 953.67 nM 20.09 298.02 nM 16.87		268.34				
9.77 uM 73.58 3.05 uM 37.91 953.67 nM 20.09 298.02 nM 16.87	59-0034		100.00	uM	-28.51	
9.77 uM 73.58 3.05 uM 37.91 953.67 nM 20.09 298.02 nM 16.87			31.25	uM	24	
3.05 uM 37.91 953.67 nM 20.09 298.02 nM 16.87			9.77	uM		
953.67 nM 20.09 298.02 nM 16.87		T	3.05	uM		
298.02 nM 16.87			953.67	nM		
93.13lnM 15.23			298.02	nM	16.87	
10.20			93.13	nM	15.23	
29.10 nM 28.83			29.10	nM	28.83	
9.09 nM 9.08			9.09	nM	9.08	
2.84 nM 23.02			2.84	nM_	23.02	
888.18 pM -0.32	<u> </u>		888.18	рΜ	-0.32	

FIG. 3H SUBSTITUTE SHEET (RULE 20)

					
59-0035	204 70				
59-0035	291.36	100.00	1.14	14.00	
39-0033		31.25		-14.92 29.17	
		9.77		15.87	-
 		3.05		18.8	
		953.67		3.88	
	-	298.02		6.15	
		93.13		3.22	
		29.10		-10.03	
	1	9.09		15.58	
		2.84		-3.56	
		888.18		-7.13	
A A					
"					
59-0036	262.31				
59-0036	202.51	100.00	uM	-0.98	
		31.25		-3.25	
		9.77		-4.54	
	-	3.05		-1.95	
		953.67		0.32	
		298.02		-6.49	
		93.13		-17.19	
		29.10	nM	-0.66	
		9.09		-5.52	
		2.84		-9.4	
		888.18	рΜ	-16.53	
OH O				·	
	į				-
					:
	į			[
59-0037	308.00	<u> </u>			
59-0037		100.00		-10.69	
		31.25		-11.99	
		9.77		-10.03	
		3.05	uM	-19.11	
		953.67		-9.4	
		298.02	nM	2.27	
		93.13		-2.9	
		29.10		-10.69	
		9.09		2.59	
		2.84		0.66	
		888.18	рм	-2.59	

FIG. 3 I SUBSTITUTE SHEET (RULE 20)

	Г		Τ		
O II					
			1		
	i				
59-0038	291.36				
59-0038		100.00		-23.430	
		31.25		-8.390	
		9.77		-0.100	
		3.05		-2.860	
		953.67		-2.240	
		298.02		3.900	
		93.13		6.350	
		29.10		1.150	
		9.09		6.960	
		2.84		-4.390	
		888.18	рм	-0.380	
l o					
Он					
	1				
CAPN	[ļ		
3 "			İ		
59-0039	710 75				
59-0039	312.35	100.00		14 170	
0000		31.25		7.620	
		9.77			
		3.05		1.940	
				-7.770	
		953.67 298.02		-5.980	
		93.13		-8.820	-
		29.10		-2.390	
		9.09		-16.580	
		2.84		-4.480	
		888.18	nM	-0.450	
		000.10	i bivi	-0.430	
					İ
0 1					
59-0040	290.37			1	
59-0040	250.37	100.00	uM	20 400	
		31.25		-20.400 -17.310	
		9.77		-8.110	
		3.05		32.180	
		953.67		36.180	\dashv
		298.02	nM nM	17.440	
		93.13	n M	2.040	
		20.13	n M	10.350	-
		29.10	niM n.i.i		
		9.09	nM oM	6.070	
		2.84	nM nM	6.960	
		888.18	ΡM	13.440	

FIG. 3J SUBSTITUTE SHEET (RULE 20)

			γ	···	
			}	[]	
HN			}]	
`` 'Ï				Ì	
CI					
O'					
Br					
59-0041	501.90	400.00	ļ.,	10.55	
59-0041_	•	100.00		-18.37	
		31.25		-17.33	
		9.77		-5.11	
		3.05		3.31 -0.77	
		953.67			
·		298.02		-1.56	·
· · · · · · · · · · · · · · · · · · ·		93.13	···	3.55 -11.24	***
			nM		
		9.09 2.84	InM InM	0.25 -0.27	
		888.18		2.02	
		000.10	l hiv	2.02	
Q					
	•				i
				!	1
59-0042	281.36				
59-0042		100.00		163.51	
		31.25		-7.67	
		9.77		9.41	
		3.05		0.75	,
		953.67		6.11	
		298.02		3.82	
		93.13		2.54	
		29.10		4.07	
·		9.09		-9.73	
		2.84	nM	-0.02	
		888.18	DΜ	18.37	
	į				ŀ
	1				
			,]	
59-0043	280.29	400.00	1.0	00.00	
59-0043		100.00		20.66	
		31.25	UM	7.4	
		9.77		-1.29	
		3.05		-2.31 1.54	
		953.67		1.54	
		298.02	nM nV	-0.79	·
		93.13		1.52	
		29.10		2.79	
		9.09	nM	-0.27	
		2.84	nM_	8.92	
<u> </u>		888.18	MU	-4.34	

FIG. 3K SUBSTITUTE SHEET (RULE 26)

					
₽ Br				[
			•	i	
	1			i	
				1	
<u> </u>	1				
0					
59-0044	341.21				
59-0044		100.00		7.38	
		31.25		11.72	
		9.77		12.49	
		3.05		-0.52	
		953.67		0.5	
		298.02		6.11	
		93.13		-1.54	
		29.10		19.14	
		9.09		. 7.13	
		2.84		-2.06	
		888.18	рМ	5.84	_
O V OH					
				1	
N N					
59-0045 H	207 77	:			
59-0045 H 59-0045	283.33	100.00	uM	52.37	64.460
00 0010	 	31.25		148.43	192.960
		9.77		204.47	422.540
		3.05		280.3	437.020
		953.67		254.82	410.890
		298.02		218.21	266.090
		93.13		196.98	183.730
		29.10		96.06	80.440
		9.09		67.35	55.530
		2.84		52.99	44.160
		2.01		02.55	1 1.100
]	
· CI			ĺ	1	
]	[
` ` ` ` ` ` ` ` ` ` ` ` ` ` ` ` ` ` ` `				1	
CI 59-0046	389.37		}]	
59-0046	009.07	100.00	luM	79.33	
		31.25		2.24	
		9.77		-1.67	
<u> </u>		3.05	luM	-6.18	
	<u> </u>	953.67		0.001	
		298.02		-3.63	
	 	93.13		-0.84	
		29.10		-8.42	
		9.09		3.92	 -
		2.84	nM	0.3	
		888.18	Ma	5.61	
		333.10	112	. 0.011	

FIG. 3L SUBSTITUTE SHEET (BIH F 2A)

			,	1	
	İ				
			Į.		
			l		
59-0047	303.37				
59-0047		100.00		-6.73	
		31.25		10.38	
		9.77		-6.16	· _ · _ · ·
		3.05		-1.39	
		953.67		-10.11	
		298.02		-4.49	
		93.13		-7.28	
		29.10		-12.34	
		9.09		-3.08	
		2.84		-2.26	
		888.18	рм	-5.34	
·	ĺ]	
		•		1	·
	Į			1	
				}	
			1]	
59-0048	384.50]	
59-0048	304.30	100.00	iiM	-6.73	
35-00-0		31.25		0.27	
· .		9.77		-5.61	
		3.05		-2.26	
	····	953.67		-12.89	
		298.02	nM	-1.69	
		93.13		-4.77	
		29.10		-8.14	
		9.09		-3.92	-
,		2.84		-11.2	
		888.18	pΜ	-4.77	
N			ľ		
			ļ.		
	İ			[
59-0049	251.29		1.		
59-0049		100.00	uМ	4.49	
		31.25		0	
		9.77	uM	-4.77	
		3.05		1.96	
		953.67	nM	8.69	
		298.02	nM	-5.04	
		93.13	nM	-2.24	
		29.10		1.69	
		9.09	nM	-4.49	
		2.84	nM	2.24	
		888.18	рМ	-0.3	

FIG. 3M SUBSTITUTE SHEET (RULE 28)

59-0050	303.36				
59-0050	303.30	100.00	uM	45.79	
0000		31.25	иM	10.02	
		9.77	uM	11.29	
		3.05		-4.68	
		953.67		-6.92	
		298.02		-5.65	
		93.13		1.69	
		29.10		7.57	
		9.09	nM	-12.05	
·		2.84	lnM	-13.63	
		888.18	рМ	5.2	
CTP STO					
50, 0051	054.75				
59-0051 59-0051	251.35	100.00	иM	32.36	
0001	 	31.25		-18.42	
	-	9.77		-0.55	
		3.05		-13.94	
		953.67		-12.02	
		298.02		-14.59	
		93.13		-7.55	
		29.10		-11.4	
		9.09		-14.91	
		2.84	nM	-10.74	
		888.18	рМ	-20.03	

FIG. 3N

SUBSTITUTE SHEET (RULE 28)

					
CI CI					
59-0052	393.28		•		
59-0052		100.00		-21.62	
		31.25	uМ	-13.32	
		9.77		-21.31	
		3.05		-11.08	
		953.67		-20.66	
·		298.02	nM .	-17.14	
		93.13	nM	-16.49	
		29.10	nM	-11.4	
		9.09	nM	-10.74	
	ļ	2.84	nM - V	-11.08	
		888.18	pΜ	-14.59	
59-0053	354.41				
59-0053		100.00	uM	-17.14	
		31.25	uM	-21.31	
		9.77	uM	-9.47	
		3.05	luM	-11.08	
		953.67	nM	-0.83	
		298.02	nM	-11.4 -9.47	
		93.13	inM	-9.47	
		29.10	nM	-19.72	
		9.09	InM	-18.45	
		2.84	InM	-10.09	
	<u> </u>	888.18	Ірм	-2.76	

FIG. 30
SUBSTITUTE SHEET (RULE 26)

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Ι γ . Ι					1
NH N					
					-
59-0054	236.28	100.00			
59-0054		100.00		-20.04	
		31.25		-6.95	
		9.77 3.05		8.3 -3.37	
		953.67		-3.37 -2.4	\dashv
		298.02		-0.99	
		93.13		-0.99	一
		29,10		-1.94	
		9.09		5.92	\dashv
	-	2.84		-2.17	
		888.18		-9.31	\neg
			<u> </u>		\dashv
Q OH	ł]	
			ļ		ŀ
HO-0					-
59-0055	425.51	100.00		47.70	
59-0055		100.00		-13.76	
		31.25		-9.51	
		9.77 3.05		-2.02 3.24	
		953.67		-6.27	1
		298.02		-4.05 -4.05	
		93.13		-1.62	
		29.10		-7.49	
		9.09		-7.09	
		2.84		-3.04	
				0.07	1
			1		- 1
1 9 7 9	1]	
O OH			1		
0 No*					
					1
			1		- 1
0.00					1
Ò					- 1
59-0056	512.34	100.00	<u> </u>		
59-0056		100.00		-1.42	
		31.25		-4.87	
		9.77		0.18 3.84	
		3.05	Jum I-M		
	 -	953.67		-5.07 -7.29	
		298.02 93.13	MIL	0.001	
	 	30,10	IHM InM	-4.25	
		29.10	IIIM	-1.02	
	 	9.09 2.84	IDM	-1.02 -3.85	
L	<u> </u>		Inw		

FIG. 3P SUBSTITUTE SHEET (RULE 28)

		 -	y · 	
, N				
				-
2~2~N].]	
59-0057 N-N		•		
59-0057	100.00	иM	-24.150	
	31.25		-24.300	
	9.77		-5.980	
	3.05		-11.500	
	953.67		-13.000	-
	298.02		-6.280	
	93.13		-12.550	<u></u>
	29.10		-6.870	
	9.09		-8.520	
	2.84		-6.320 -16.290	
	2.04	111 V I	- 10.290	
O S N				
\ \^0\\\S\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\	[
· _/				
FO. 00FO			· I	4-
59-0058	100.00			
59-0058	100.00		4.170	·
	31.25		7.620	*1
•	9.77		-1.790	· · · · · · · · · · · · · · · · · · ·
	3.05		-7.320	
	953.67		-1.940	44.
	298.02		-6.870	•
	93.13		-1.490	•
	29.10		-8.370	
	9.09	nM	-5.080	
	2.84	nM	-12.400	
	1		Ì	
N-CI				
S S N N S				
I N S	ļ		İ	
.,	İ			
59-0059				
59-0059	100.00	uM	-18.700	
,	31.25		-16.140	
	9.77	uM	-3.090	
	3.05	υM	0.150	
	953.67		6.010	
	298.02		-1.910	
	93.13		-1.760	
	29.10	nM	-9.100	
	9.09	nM	-8.220	
	2.84	nM	-5.720	
	:			

FIG. 3Q SUBSTITUTE SHEET (RULE 26)

N-N S S				
N S S				
DH 0000 OH	1 .			
59-0060	100.00		4.350	
59-0060			-4.250 -14.520	
<u> </u>	31.25 g			
ļ 	3.05		1.030 -1.180	
	953.67		-13.200	
	298.02		-0.740	
	93.13		-3.670	
	29.10		-7.340	
	9.09		-1.310	
	2.84		0.290	
	2.041	1 5171	0.250	
-s L	1			
N HO HO				
" " "			ļ	
59-0061		j	1	
59-0061	100.00	uM.	-17.890	
00 0001	31.25		-18.770	
	9.77	ı tM	-17.170	 -
	3.05		-14.080	
	953.67		-17.020	
	298.02		-7.190	
	93.13	nM	-1.910	
	29.10		-0.440	
· · · · · · · · · · · · · · · · · · ·	9.09		-6.010	
	2.84		-4.560	
				_
		ļ		
	İ			
NH N				
N _N N-C ₁				
\ _\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \				
	[
59-0062				
59-0062	100.00		-13.940	
ļ	31.25		-12.910	_ .
	9.77		-4.560	
	3.05	uM	-4.540	
	953.67	nM	-6.900	<u></u>
	298.02		-4.100	
ļ	93.13		-1.620	;
	29.10	nM	3.230	

FIG. 3R SURSTITUTE SHEET (BUH F 2R)

	9.09 nM	8.070
	2.84 nM	0.440
	2.04 (114)	0.440
N N N		
H [N]		
59-0063	1	
59-0063	100.00 uM	
	31.25 uM	-2.510
	9.77 uM	-6.130
	3.05 uM	-8.950
		-8.020
	953.67 nM	-8.010
	298.02 nM 93.13 nM	-2.520
	93.13 HM	-5.810
	29.10 nM	-3.450
	9.09 nM 2.84 nM	-4.390
	2.04 [nM	-6.280
		1
N		
59-0064		
59-0064	100 00 11	
35-0004	100.00 luM	-23.090
	31.25 uM	-21.040
	9.77 uM	78.400
	3.05 uM	155.220
	953.67 nM	113.120
	298.02 nM	30.640
	93.13 nM	15.240
	29.10 nM	22.150
	9.09 nM	-0.770
	2.84 nM	4.410
		1 1
		i
	<u> </u>	
OH N		
59-0065		1
59-0065	100 00 11	
03 0000	100.00 UM	-2.030
	31.05 uM	-2.980
	9.77 uM	-15.240
	3.05 uM	-15.400
	953.67 nM	-15.240
	298.02 nM	-10.520
	93.13 nM	-13.830
	29.10 nM	-5.810
	9.09 nM	-3.620
I	2.84 nM	-7.070

FIG. 3S SUBSTITUTE SHEET (RULE 20)

			
H ₂ N			
59-0066			
59-0066	100.00 uk		
	31.25 uk		
	9.77 uN		
	3.05 uM		
	953.67 nk		
	298.02 nk	3.780	
	93.13 nN		
	29.10 nk		
	9.09 nA 2.84 nA	4 -2.820 4 -3.920	
	∠.04 nn	vi -3.920	
]			
			Ì
			Į
H			
59-0067			
59-0067	100.00 ul		
	31.25 u		
	9.77 ul		
	3.05 ut		
	953.67 nl		
	298.02 nl	M 75.330	
	93.13 nl		
	29.10 nl		
	9.09 nl 2.84 nl		
	2.04 Ni	M 4.45U	
5 2			
N N			
•	•		
59-0068 59-0068	100.00 u	M -22.130	
03 0300	31.25 u		
	9.77 u		
	3.05 u	M 81.060	
	953.67 n	M 22.330	
	298.02 n	M 17.300	
	93.13 n	M 8.460	
	29.10 n	_{IM} -3.530	
	9.09 n	M -4.230	
	2.84 n	M -6.140	

FIG. 3T SUBSTITUTE SHEET (RULE 26)

HO		 -			
100.00 LM	НО				
100.00 LM	o l				
31,25 uM 9,670 9,77 uM 16,090 3,05 uM -7,180 953,67 nM -2,840 298,02 nM -3,710 93,13 nM -11,180 59-0070 100,00 uM -25,930 2,84 nM -4,750 3,05 uM 214,280 953,67 nM 158,530 298,02 nM 72,890 93,13 nM 20,940 29,10 nM 7,760 9,09 nM 7,590 298,02 nM 7,590 298,04 nM -8,400 100,00 uM -18,650 100,00 uM -18,650 100,00 uM -18,650 100,00 uM -18,650 100,00 uM -18,650 100,00 uM -18,650 100,00 uM -16,610 100,00 uM -16,610 100,00 uM -16,610 100,00 uM -16,610 100,00 uM 176,090 100,00 uM 176,090 100,00 uM 176,090 100,00 uM 176,090 100,00 uM 176,090 100,00 uM 176,090 100,00 uM 176,090 100,00 uM 176,090 100,00 uM 176,090 100,00 uM 176,090 100,00 uM 176,070 100,00 uM 176,090		100.00		5 400	
9.77 LM 16.090 3.05 LW -7.180 9.53.67 lm -2.840 298.02 lm -3.710 9.3.13 lm -11.180 299.01 lm -5.790 9.09 lm -7.180 9.09 lm -7.180 2.84 lm -7.180 2.84 lm -7.180 2.84 lm -7.180 2.84 lm -7.180 2.84 lm -7.180 2.84 lm -7.180 2.84 lm -7.180 2.84 lm -7.180 2.84 lm -7.180 2.84 lm -7.180 2.84 lm -7.180 2.84 lm -7.180 2.84 lm -7.180 2.84 lm -7.180 2.84 lm -7.180 2.84 lm -7.180 2.85 lm -7.180 2.85 lm -7.180 2.86 lm -7.180 2.87 lm -7.180 2.89 lm -7.180 2.89 lm -7.180 2.89 lm -7.180 2.89 lm -7.180 2.89 lm -7.180 2.89 lm -7.180 2.84 lm -8.400 2.84 lm -8.400 2.85 lm -7.500 2.86 lm -7.500 2.87 lm -7.500 2.88 lm -7.500 2.88 lm -7.500 2.88 lm -7.500 3.05 lm -7.600 3.05 lm -7.600 3.05 lm -7.600 3.05 lm -7.600 3.05 lm -7.600 3.05 lm -7.600 3.05 lm -7.600 3.05 lm -7.600 3.05 lm -7.600 3.05 lm -7.600 3.05 lm -7.600 3.05 lm -7.600 3.05 lm -7.600 3.05 lm -7.600 3.05 lm -7.600 3.05 lm -7.600 3.05 lm -7.600	59-0069				
3.05 uM					
953.67 nM -2.840 298.02 nM -3.710 93.13 nM -11.180 29.10 nM -5.790 9.09 nM -7.180 2.84 nM -4.750 59-0070 100.00 uM -25.930 2.84 nM -23.000 31.25 uM -23.000 9.77 uM 36.060 3.05 uM 214.280 953.67 nM 158.530 298.02 nM 72.890 93.13 nM 20.940 29.10 nM 7.760 9.09 nM 7.590 298.02 nM 7.590 2.84 nM -8.400 100.00 uM -18.650 9.09 nM -8.400 100.00 uM -18.650 9.09 nM -8.400 100.00 uM -18.650 9.09 nM -8.400 100.00 uM -15.540 9.09 nM -8.400 100.00 uM -15.540 9.77 uM 17.060 3.05 uM 176.090 953.67 nM 76.070 298.02 nM 76.070 298.02 nM 731.260					
298.02 nM					
93.13 nM -11.180 29.10 nM -5.790 9.09 nM -7.180 2.84 nM -4.750 59-0070 100.00 uM -25.930 31.25 uM -23.000 9.77 uM 36.060 3.05 uM 214.280 953.67 nM 158.530 298.02 nM 72.890 93.13 nM 20.940 29.10 nM 7.760 9.09 nM 7.590 2.84 nM -8.400 100.00 uM -18.650 9.09 nM -7.590 2.84 nM -8.400					
29.10 nM					
9.09 nM					
2.84 nM					
59-0070 59-0070 100.00 uM -25.930 31.25 uM -23.000 9.77 uM 36.060 3.05 uM 214.280 953.67 lnM 158.530 298.02 lnM 72.890 93.13 lnM 20.940 29.10 lnM 7.760 9.09 lnM 7.590 2.84 lnM -8.400 100.00 uM -18.650 2.84 lnM -8.400 100.00 uM 170.00 2.84 lnM -8.400 100.00 uM 170.00 2.84 lnM -8.400 100.00 uM 170.00 2.84 lnM -8.400 100.00 uM 170.00 2.84 lnM -8.400 100.00 uM 170.00 2.84 lnM -8.400		9.09	nM		-
100.00 uM -25.930 31.25 uM -23.000 9.77 uM 36.060 3.05 uM 214.280 953.67 nM 158.530 298.02 nM 72.890 93.13 nM 20.940 29.10 nM 7.760 9.09 nM 7.590 2.84 nM -8.400 31.25 uM -15.540 9.77 uM 17.060 9.77 uM 17.060 9.77 uM 17.060 9.77 uM 176.090 953.67 nM 76.070 298.02 nM 31.260 93.13 nM 16.410		2.84	nM	-4./50	
100.00 M	CTS-H				
31.25 uM	59-0070				
9.77 uM 36.060 3.05 uM 214.280 953.67 nM 158.530 298.02 nM 72.890 93.13 nM 20.940 29.10 nM 7.760 9.09 nM 7.590 2.84 nM -8.400 59-0071 100.00 uM -18.650 31.25 uM -15.540 9.77 uM 17.060 3.05 uM 176.090 953.67 nM 76.070 298.02 nM 31.260 93.13 nM 16.410					
3.05 uM 214.280 953.67 nM 158.530 298.02 nM 72.890 93.13 nM 20.940 29.10 nM 7.760 9.09 nM 7.590 2.84 nM -8.400 59-0071 59-0071 100.00 uM -18.650 31.25 uM -15.540 9.77 uM 17.060 3.05 uM 176.090 953.67 nM 76.070 298.02 nM 31.260 93.13 nM 16.410		31.25	uM		
953.67 nM 158.530 298.02 nM 72.890 93.13 nM 20.940 29.10 nM 7.760 9.09 nM 7.590 2.84 nM -8.400 59-0071 59-0071 100.00 uM -18.650 9.77 uM 17.060 9.77 uM 17.060 3.05 uM 176.090 953.67 nM 76.070 298.02 nM 31.260 93.13 nM 16.410					* .
298.02 nM 72.890					
298.02 nM		953.67	nM		
93.13 nM 20.940 29.10 nM 7.760 9.09 nM 7.590 2.84 nM -8.400 59-0071 100.00 uM -18.650 31.25 uM -15.540 9.77 uM 17.060 3.05 uM 176.090 953.67 nM 76.070 298.02 nM 31.260 93.13 nM 16.410					
9.09 nM 7.590 2.84 nM -8.400 59-0071 59-0071 100.00 uM -18.650 31.25 uM -15.540 9.77 uM 17.060 3.05 uM 176.090 953.67 nM 76.070 298.02 nM 31.260 93.13 nM 16.410					
2.84 nM -8.400 59-0071 59-0071 100.00 uM -18.650 31.25 uM -15.540 9.77 uM 17.060 3.05 uM 176.090 953.67 nM 76.070 298.02 nM 31.260 93.13 nM 16.410		29.10	nM		
59-0071 59-0071 100.00 uM -18.650 31.25 uM -15.540 9.77 uM 17.060 3.05 uM 176.090 953.67 nM 76.070 298.02 nM 31.260 93.13 nM 16.410		9.09	nM		
59-0071 100.00 uM -18.650 31.25 uM -15.540 9.77 uM 17.060 3.05 uM 176.090 953.67 nM 76.070 298.02 nM 31.260 93.13 nM 16.410		2.84	nM	-8.400	
59-0071 100.00 uM -18.650 31.25 uM -15.540 9.77 uM 17.060 3.05 uM 176.090 953.67 nM 76.070 298.02 nM 31.260 93.13 nM 16.410	CYN O				
59-0071 100.00 uM -18.650 31.25 uM -15.540 9.77 uM 17.060 3.05 uM 176.090 953.67 nM 76.070 298.02 nM 31.260 93.13 nM 16.410	59-0071		<u> </u>		
9.77 uM 17.060 3.05 uM 176.090 953.67 nM 76.070 298.02 nM 31.260 93.13 nM 16.410					
3.05 uM 176.090 953.67 nM 76.070 298.02 nM 31.260 93.13 nM 16.410					
3.05 uM 176.090 953.67 nM 76.070 298.02 nM 31.260 93.13 nM 16.410		9.77	uM		
953.67 nM 76.070 298.02 nM 31.260 93.13 nM 16.410				176.090	
298.02 nM 31.260 93.13 nM 16.410		953.67	nM	76.070	
93.13 nM 16.410		298.02	nM		
20 10 - 4 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1		93.13	nM	16.410	
		29.10	nM	4.870	
9.09 nM -7.330		9.09	пM		
2.84 nM -4.660		2.84	nM	-4.660	

FIG. 3U SUBSTITUTE SHEET (RULE 20)

			
N S			
S H Q	 		
59-0072			1
59-0072	100.00	uM -19.750	
	31.25		
	9.77		
	3.05		
	953.67		
	298.02		
	93.13		
	29.10	nM 213.580	
	9.09	nM 164.320	
	2.84		
	888.18	pM 60.770	
F I			
F			i
N N F			
F	l		
F	j i		
F			}
50 0077			
59-0073 59-0073	100.00	7.010	
39-0073	100.00		
-	31.25		
	9.77 3.05		
	953.67		
	298.02		
	93.13		
	29.10		
	9.09		
	2.84	nM 5.3	
F CI CL F	2.01	3.0	<u> </u>
		1	
N=V=V			
CI———			
		1	
59-0074 F F			
59-0074	100.00	uM -2.85	
	31.25	uM 2.14	<u> </u>
	9.77	uM -4.85	
	3.05		
	953.67		
	298.02		
	93.13	nM 4.47	
	29.10	nM -8	
	9.09		
	2.84		
		3.07	

FIG. 3V SUBSTITUTE SHEET (RULE 28)

				
			[j
r N N N F				
F =N H (N-F	1 !			
_0,			ŀ	
			į.	ļ
59-0075 H				
59-0075	100.00	uM	-0.68	
	31.25		-10.16	
	9.77		-5.35	
	3.05	υM	-6.5	
	953.67	nM	-0.85	
	298.02	nM	5.97	
	93.13	nM	0.97	
	29.10		-2.35	
	9.09	nM	0.32	
	2.84	nM ·	10.47	
			!	
F CI CL F				
F		1		
' N N				
—OH ,		1		
	•	1	•	
59-0076	100.00		10.40	•
59-0076	100.00		-19.12	
	31.25	uM .	9.29	
	9.77	UM	10.63 22.43	
	3.05	UM		
	953.67	InM	19.93 3.47	
	298.02	nm M	19.93	
	93.13		10.63	
	29.10		14.28	
	9.09 2.84	nM		
	2.04	INM.	11.3	
F 0.				
F_F_CI		1		
	ĺ		i	
N N N N F	İ			
\ __________________\			.	
59-0077 CI F			1	,
59-0077	100.00	luM	-20.96	
03 0077	31.25		-16.23	
	9.77	uM	-10.58	
	3.05		-11.96	···
	953.67	nM	-19.44	
	298.02	nM	-17.3	
	93.13	nM	-13.79	
	29.10		-15.62	
	9.09	nM	-14.09	
	2.84	nM	-14.4	
	2.04	1	1 10 71	

FIG. 3W SUBSTITUTE SHEET (RULE 20)

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			·
		İ	
NO NEW	1		
			1
59-0078			
59-0078	100.00		
	31.25		<u> </u>
	9.77		
	3.05		L
	953.67		
	298.02		
	93.13		
	29.10		
	9.09		
	2.84	nM 56.600	
	888.18	pM 92.520	
	1		
59-0079			
59-0079	100.00		
	31.25	uM –21.390	
	9.77		
	3.05		
	953.67		
	298.02	nM 64.000	
	93.13	nM 46.490	·
	29.10	nM 30.310	
	9.09	nM 33.490	
	2.84	nM 29.760	
	l l		
	j		
N N N N N N N N N N N N N N N N N N N			
59-0080			
59-0080	100.00	uM 5.390	
	31.25		
	9.77	uM 6.440	
	3.05	uM 2.440	
	953.67	nM -5.030	
	298.02	nM 7.660	
	93.13	nM -3.630	
	29.10	nM 3.650	
	9.09	nM 1.050	
	2.84		
		3.3.0	
		l i	
59-0081		1	
139-0001] 1	ì	1

FIG. 3X Substitute sheet (rule 26)

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100.00 M	
9.77 uM -8.670 3.05 uM 2.440 953.67 nM -5.200 298.02 nM -2.080 93.13 nM 1.220 29.10 nM -2.250 9.09 nM 1.050 2.84 nM -3.300 H N N S S S S S S S S S S S S S S S S	
3.05 uM 2.440 953.67 nM -5.200 298.02 nM -2.080 93.13 nM 1.220 29.10 nM -2.250 9.09 nM 1.050 2.84 nM -3.300 59-0082 100.00 uM 111.79 31.25 uM 62.68 9.77 uM 32.36 9.77 uM 32.36 3.05 uM 9.11 953.67 nM -10.62 298.02 nM -1.86 93.13 nM -6.89 29.10 nM -3.91	
953.67 nM -5.200 298.02 nM -2.080 93.13 nM 1.220 29.10 nM -2.250 9.09 nM 1.050 2.84 nM -3.300 59-0082 100.00 uM 111.79 31.25 uM 62.68 9.77 uM 32.36 3.05 uM 9.11 953.67 nM -10.62 298.02 nM -1.86 93.13 nM -6.89 29.10 nM -3.91	
298.02 nM	
93.13 nM 1.220 29.10 nM -2.250 9.09 nM 1.050 2.84 nM -3.300 59-0082 100.00 uM 111.79 31.25 uM 62.68 9.77 uM 32.36 9.77 uM 32.36 3.05 uM 9.11 953.67 nM -10.62 298.02 nM -1.86 93.13 nM -6.89 29.10 nM -3.91	
29.10 nM -2.250 9.09 nM 1,050 2.84 nM -3.300 59-0082 59-0082 100.00 uM 111.79 31.25 uM 62.68 9.77 uM 32.36 9.77 uM 32.36 3.05 uM 9.11 953.67 nM -10.62 298.02 nM -1.86 93.13 nM -6.89 29.10 nM -3.91	
9.09 nM 1.050 2.84 nM -3.300 59-0082 59-0082 100.00 uM 111.79 31.25 uM 62.68 9.77 uM 32.36 9.77 uM 32.36 3.05 uM 9.11 953.67 nM -10.62 298.02 nM -1.86 93.13 nM -6.89 29.10 nM -3.91	
2.84 nM -3.300 59-0082 59-0082 100.00 uM 111.79 31.25 uM 62.68 9.77 uM 32.36 3.05 uM 9.11 953.67 nM -10.62 298.02 nM -1.86 93.13 nM -6.89 29.10 nM -3.91	
59-0082 59-0082 100.00 uM 111.79 31.25 uM 62.68 9.77 uM 32.36 3.05 uM 9.11 953.67 nM -10.62 298.02 nM -1.86 93.13 nM -6.89 29.10 nM	
59-0082 100.00 uM 111.79 31.25 uM 62.68 9.77 uM 32.36 3.05 uM 9.11 953.67 nM -10.62 298.02 nM -1.86 93.13 nM -6.89 29.10 nM -3.91	
59-0082 100.00 uM 111.79 31.25 uM 62.68 9.77 uM 32.36 3.05 uM 9.11 953.67 nM -10.62 298.02 nM -1.86 93.13 nM -6.89 29.10 nM -3.91	
59-0082 100.00 km 111.79 31.25 km 62.68 9.77 km 32.36 3.05 km 9.11 953.67 km -10.62 298.02 km -1.86 93.13 km -6.89 29.10 km -3.91	
59-0082 100.00 km 111.79 31.25 km 62.68 9.77 km 32.36 3.05 km 9.11 953.67 km -10.62 298.02 km -1.86 93.13 km -6.89 29.10 km -3.91	
59-0082 100.00 km 111.79 31.25 km 62.68 9.77 km 32.36 3.05 km 9.11 953.67 km -10.62 298.02 km -1.86 93.13 km -6.89 29.10 km -3.91	
59-0082 100.00 km 111.79 31.25 km 62.68 9.77 km 32.36 3.05 km 9.11 953.67 km -10.62 298.02 km -1.86 93.13 km -6.89 29.10 km -3.91	
59-0082 100.00 km 111.79 31.25 km 62.68 9.77 km 32.36 3.05 km 9.11 953.67 km -10.62 298.02 km -1.86 93.13 km -6.89 29.10 km -3.91	
31.25 uM 62.68 9.77 uM 32.36 3.05 uM 9.11 953.67 nM -10.62 298.02 nM -1.86 93.13 nM -6.89 29.10 nM -3.91	
9.77 uM 32.36 3.05 uM 9.11 953.67 nM -10.62 298.02 nM -1.86 93.13 nM -6.89 29.10 nM -3.91	
3.05 uM 9.11 953.67 nM -10.62 298.02 nM -1.86 93.13 nM -6.89 29.10 nM -3.91	
953.67 nM -10.62 298.02 nM -1.86 93.13 nM -6.89 29.10 nM -3.91	
298.02 nM -1.86 93.13 nM -6.89 29.10 nM -3.91	
93.13 nM -6.89 29.10 nM -3.91	
29.10 nM -3.91	
9.09 nM 2.22	
2.84 nM 16.36	
	•
	•

	••
SAN	
59-0083	
59-0083 100.00 uM 48.93	
31.25 uM 40.91	
9.77 uM 25.85	
3.05 uM 17.85	
953.67 nM 8.55	
298.02 nM 3.9	
93.13 nM 2.05	
29.10 nM 7.99	
9.09 nM -3.91	
2.84 nM 3.35	
" 0 \ \ \ \	
59-0084	
59-0084 100.00 uM 37.670	
31.25 uM 26.050	
9.77 uM 9.210	

FIG. 3Y SUBSTITUTE SHEET (RULE 26)

	·		
	953.67 nl		
	298.02 nl	M 5.900	
	93.13 ni		
	29.10 nl		
	9.09 nl	M 10.080	
	2.84 nl	M -2.080	
I Г			
			J
" " " Т.он Т			
59-0085			
59-0085	100.00 ul		
	31.25 uk		
	9.77 uk		
	3.05 uk		
	953.67 nk		
	298.02 nA		
	93.13 lnN		
	29.10 nk		
	9.09 nA	M -0.760	
	2.84 nk	M 5.940	
	1		
			1
			1
0 V OH			
59-0086 Ö			
59-0086	100.00 uM	d 30.750	
	31.25 uM		 -
	9.77 uM		
	3.05 uM		
	953.67 nM		
	298.02 nM		
	93.13 nM		
	29.10 nM		
	9.09 nM		
	2.84 nM		
			}
" O NH2			
l			1
59~0087			
59-0087	100.00 uM		
	31.25 uM	11.080	
	9.77 uM	3.100	
	3.05 luM	1 -1.320	
	953.67 nM	17.070	
	298.02 nM	7.950	
	93.13 nM		
	29.10 nM	4.510	
	9.09 nM		
	2.84 nM	9,660	

FIG. 3Z Substitute sheet (rule 28)

			T***	
Н				
NH2				
U NII2]		
59-0088		1	1	
59-0088	100.00	uM		
	31.25			
	9.77		 	
	3.05			
	953.67		 	
	298.02	InM	 	
	93.13	pМ	 	
	29.10		 	······································
	9.09			
	2.84	nM		
· · · · · · · · · · · · · · · · · · ·	2.04	ITIM	 	
	Į.	1 '		
		1	.	
	1	1	'	
		j ·	1	
59-0089				·
59-0089	100.00	иM	60.09	
	31.25		116.25	
	9.77		65.85	
	3.05		36.1	
	953,67		37.96	
	298.02		18.42	
	93.13	InM	6.33	
	29.10		13.58	
			0.75	
	9.09	INM - M		
	2.04	INM .	-5.77	·
		·	-	•
	.		·	•
	••			
		l ·	!	•
7		1		
59-0090				
59-0090	100.00		32.77	
	31.25		24.63	
	9.77	uM	19.5	
	3.05	uM_	41.31	
	953.67	nM	9.8	
	298.02	lnM	-1.76	
	93.13	InM	3.53	
	29.10	nM	2.95	
	9.09 2.84	InM	2.95 2.95 7.8	
	2.84	InM	/.8	
	1	l		
	, .			
			1	
59-0091				
59-0091 59-0091	100.00 31.25		0.26 13.54	

FIG. 3AA SUBSTITUTE SHEET (RULE 26)

	1 233	1.11	75.71	
	9.77		95.94	
	3.05		87.71	
	953.67		44.17	
	298.02	nM_	38.26	
	93.13		23.87	
	29.10	nM	21.65	
	9.09	nM	10.95	
	2.84	nM	20.92	
	ļ			
59-0092				
59-0092	100.00	uM	-11.56	
	31.25		17.84	
	9.77		50.19	
	3.05		25.84	
	953.67		14.4	
	298.02		6.77	•
	93.13		8.62	
	29.10		2.22	_
	9.09		8.38	
	2.84	nM	1	
59-0093	100.00		11.07	
59-0093	100.00		-11.67	
	31.25		15.02	
	9.77		35.44	
· · · · · · · · · · · · · · · · · · ·	3.05		29.89	
	953.67		22.88 19.56	
	298.02			
	93.13		5.18	
	29.10		7.39 4.56	
	9,09 2.84	nM nV	5.9	
		nm .	3.9	
59-0094				
59-0094	100.00		-17.69	
	31.25	uM.	45.15	
	9.77	υM	24.97	
	3.05	นM	19.81	
	953.67		9:35	
	298,02		1.36	
	93.13		9.24	
	29.10	nM	-0.48	
	9.09 2.84	nM	6.16	
L	2.84	IDM	1.61	

FIG. 3BB SUBSTITUTE SHEET (RULE 28)

			·		,
HO 0		1			
N.		İ			
		j			
N. W.		1	i	1	
н 0					
59-0095	-				
59-0095		100.00	uM		44.7
		31.25			47.61
		9.77			12.78
		3.05			21.49
		953.67			15.01
		298.02	nM		10.22
		93.13	nM		13.98
		29.10			20.31
		9.09	nM		10.9
		2.84	nM		9.21
HOO			}		
1]	
					.
					.
N N					
59-0096					
59-0096	*	100.00	uМ		413.05
		31.25			287.23
		9.77		·	137.38
·		3.05			78.5
•		953.67			49.13
		298.02	nM		50.68
		93.13			47.95
,		29.10			26.28
		9.09	nM		18.75
		2.84	nM		22.17
H00	i				. [
"" \ \ \ \					
					· · · · · · · · · · · · · · · · · · ·
H S			į		1
" 5 N					
150,0007	1]
59-0097		100.00			
59-0097	·	100.00			77.47
		31.25			201.9
		9.77	UM UM		160.93 61.44
		3.05 953.67			47.78
		298.02			51.54
		93.13	nM		34.64
		29.10	nM		43.18
		29.10 9.09 2.84	nM		39.91
	·	2.84	nM		27.13

FIG. 3CC SUBSTITUTE SHEET (RULE 26)

\mathbf{r}	_	1	1	71
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S	37 174			
H00			1 1	
		ļ		
H M				
			1	
H Ö			1	
59-0098				
59-0098	100.00			-1.38
	31.25			186.89
	9.77		<u> </u>	221.7
-	3.05			164.69
	953.67 298.02			96.94 68.25
	93.13		 	57 57
	29.10		 	51.88
	9.09		 	41.29
	2.84	nM		33.43
⇒ N			 	
		[
, N			!	
59-0099]		,
59-0099	100.00		17.040	
0000	31.25		13.040 56.880	
	9.77		119.340	
	3.05		237.420	
	953.67		285.440	
	298.02		164.610	
	93.13		123.300	
	29.10		69.240	
	9.09	nM	44.500	
	2.84	nM	47.390	
_ N	,			
		-		
H CI				
59-0100				
59-0100	100.00	rdV	10.000	
0.00	31,25		-10.020 -10.730	
	9.77		30.340	
	3.05	иМ	114.410	
	953.67		77.540	
	298.02	nM	40.290	
	93.13	nM	35.730	
	29.10	nM	28.290	
	9.09 2.84	nM nV	17.480	
c F		I HVI	11.470	
l ^t ,L _F				•
	}			
HN N-			ĺ	
59-0101				
59-0101	100.00	uM	26.370	

FIG. 3DD SUBSTITUTE SHEET (BINE 2A)

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		74.05	T		
		31.25		12.440	
		9.77		-0.780	
	<u> </u>	3.05		10.280	
		953.67	InM	2.110	
		298.02	lnM	7.860	
		93.13		1.140	
		29.10		2.820	
	_	9.09	nM	4.150	
		2.84	nM	5.590	
	1 . 1				
_ N	1				
				1 . 1	
s '_s	1		ŀ		
	1.			.]	
V			1	1	
59-0102	284.34		i	1	
59-0102		100.00	иM	-24.350	
		31.25		-11.140	
		9.77		63.540	
		3.05		121.320	
		953.67		79.530	
		298.02		72.460	
		93.13		66.290	 -
		29.10		45.690	
				27.260	
		9.09 2.84	nM	42.330	
		888.18	I DM	33.430	.
		000.10	I LUAI	33.430	
N O O		•			
] }	
l H H L] '	•••
59-0103	313.38	•		i !	. •
	1 0,0.00	100.00	uM	-29.69	
		31.25		-29.53	
		9.77		-28.22	
		3.05		-27.72	
	+	953.67		-5.58	
	 	298.02		54.15	
	 	93.13	nM	170.95	
	 				 -
	 	29.10		222.87	
	+	9.09	nM nM	210.39	
		2.84		203.4	·
		0.80	nM	114.55	
~ N · O O′				.	
		ļ	ı	- · ·	-
N N N	1				
FO 0104 H H					•
59-0104	297.31				
		100.00		-29.84	
		31.25		-26.72	
		9.77	uM	-29.2	
·		3.05	uM	-27.05	
······································		953.67		24.37	
		298.02	nM	196.42	
		93.13		213.89	

FIG. 3EE Substitute sheet (rule 20)

		29.10		220.04	
		9.09	nM	245.42	
		2.84		182.45	
		0.80	nM	119.55	
			}		
	1				
H H DO	1		ļ		
н н ✓∕О∕	1		}		
			ļ		
59-0105	267.29				
	<u> </u>	100.00		-25.72	
		31.25		-15.89	
		9.77		31.7	
		3.05		54.17	
		953.67	nM	53.67	
		298.02	InM	41.35	
	<u> </u>	93.13		44.5	
	 	29.10		39.02	
		9.09		25.38	
	 	2.84	<u> </u>	31.7	
		0.80	nM	18.05	
N Ö					
				1	
N N I					
59-0106	297.31				
00 0100	207.01	100.00	иM	-14.05	_
		31.25		223.52	
		9.77		202.58	
·		3.05		107.73	
	1	953.67		71.3	_
		298.02		44.84	
		93.13		26.54	_
		29.10		23.05	
		9.09		27.87	
		2.84		12.23	
		0.80		11.4	_
110					_
H0 \ 0					
	i				
l H Ö 🖟					
59-0107	332.38				
		100.00	υM	48.55	_
		31.25	uM	22.87	
		9.77	uM	7.19	_
		3.05	υM	0.65	_
		953.67		11.12	
	1	298.02		-3.92	
	 	93.13		1.09	
		29.10	InM	-15.69	

FIG. 3FF SUBSTITUTE SHEET (FULE 26)

		298.02	nM	15.24
		953.67	nM	25.26 27.01
		9.77 t	IM I	35.27
		31.25		67.05
		100.00	JM ML	65.11
59-0110	286.29			
'' U]	ļ	
HOO				
		2.84 0.80	nM	6.98
		2.84	nM	-4.58
		9.09		5.01
		29.10		-3.27
		93.13		3.71
		953.67 298.02		13.51 7.85
		3.05		6.32
		9.77		5.89
		31.25		27.64
· .		100.00		43.12
59-0109	316.31			
Ť				
H O				
N N				
H0 \ \ 0				
		0.00		1,17
		0.80		4.14
	 	2.84	nM	3.92
	 	29.10 9.09		2.62 -4.8
		93.13		-4.8 2.63
	 - 	298.02	nM	25.68
	 	953.67	nM	18.94
		3.05		37.23
		9.77		58.57
		31.25	uM	96.02
		100.00		227.73
59-0108	316.31		1	
H 0 6			ĺ	
]	•	}	1
H0 \(\rho \)				
		0.80	nM	-16.11
		2.84	nM	-2.62
		9.09	ILIM	-11.32

FIG. 3GG SUBSTITUTE SHEET (RULE 26)

	07.47	1	T	
				
 				
				
	0.80	InM	4.14	
152.15				
	100.00	uM	23.360	
	9.77	uM		
	3.05	uM	5.390	
	953.67	nM	2.190	
			1.230	
			2.430	
			6.350	
	9.09	nM	4.350	
	2.84	nM	4.350	
	0.80	nM	3.230	
149.19			1	
	100.00	υM	2.670	
	31.25	uM	4.670	
			2.750	
	3.05	uM	3.790	
	953.67	nM	4.270	
	298.02	nM	1.150	
	93.13	nM	9.630	
	29.10	nM	0.920	
			0.510	
<u> </u>			12.900	
	0.80	nM	2.990	
274.37				
			22.010	
			25.940	
 				
	953.67	nM	-0.760	
	300.07	11171	/ 444	
	298.02	nΜ	-4.690	
	298.02 93.13	nM nM	-4.790	
	298.02 93.13 29.10	nM nM nM	-4.790 5.090	
	298.02 93.13	nM nM nM nM	-4.790	
		152.15 152.15 100.00 31.25 9.77 3.05 953.67 298.02 9.10 9.09 2.84 0.80 149.19 100.00 31.25 9.77 3.05 953.67 298.02 9.77 3.05 953.67 298.02 9.77 3.05 953.67 298.02 9.77 3.05 953.67 298.02 9.77 3.05	100.00 uM 31.25 uM 9.77 uM 3.05 uM 953.67 nM 298.02 nM 93.13 nM 29.10 nM 9.09 nM 2.84 nM 0.80 nM 149.19 100.00 uM 31.25 uM 953.67 nM 298.02 nM 953.67 nM 298.02 nM 953.13 nM 2910 nM 909 nM 284 nM 0.80 nM 274.37	152.15 100.00 uM 23.360 31.25 uM 22.330 9.77 uM 12.260 3.05 uM 2.330 953.67 nM 2.190 298.02 nM 4.350 2.84 nM 4.350 2.84 nM 4.350 2.84 nM 4.350 3.125 uM 3.230 3.125 uM 4.670 3.125 uM 3.790 3.13 nM 3.2430 3.13 nM 3.230 3.13 nM 3.230 3.13 nM 3.230 3.13 nM 3.230 3.13 nM 3.230 3.13 nM 3.230 3.13 nM 3.230 3.13 nM 3.230 3.13 nM 3.230 3.13 nM 3.230 3.13 nM 3.230 3.13 nM 3.230 3.13 nM 3.230 3.35 uM 3.790 3.355 uM 3.790 3.355 uM 3.790 3.355 uM 3.790 3.355 uM 3.230 3.230 3.230 3.355 uM 3.230 3.230 3.355 uM 3.230 3.230 3.355 uM 3.230 3.230 3.355 uM 3.230 3.230 3.355 uM 3.230 3.230 3.355 uM 3.230 3.230 3.355 uM 3.230 3.355 uM 3.230 3.355 uM 3.230 3.355 uM 3.3070 3.355 uM 3.3070 3.30

FIG. 3HH Substitute sheet (rule 26)

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	38/174				
N-S 0=\$=0 0 0					
No*					
1	475.54			1	
59-0114	4/3.34	100.00	· M	52.030	
		31.25		36.120	
		9.77	1111	25.840	
		3.05		16.670	
	 -	953.67		12.540	
		298.02	nM	9.420	
		93.13		-1.060	
		29.10		2.160	
		9.09		-6.000	
		2.84	nM	2.470	
		0.80	nM	-1.460	-
CI			-		-
N-CI N-SI					V#F
59-0115	318.87				. · ·
		100.00	uM	73.700	
		31.25		2.770	
		9.77		-10.430	
		3.05		-12.340	
		953.67		-13.750	
		298.02		-13.960	·
		93.13	nM	-11.940	
		29.10		-9.830	
		9.09		-8.820	.,
·		2.84	nM	-0.950	
		0.80	nM	-0.050	
OH NACT N					
59-0116	269.30				
		100.00		31.380	
		31.25		109.060	
		9.77		231.070	
		3.05		240.670	
		953.67		132.020	
		298.02	nM	75.820	
		93.13		53.250	
		29.10	nM	47.500	
		9.09 2.84	INM.	39.440 42.170	
		0.80	nM	31.180	
CIS N			IIM	31.100	
59-0117	268.38			60 500	
	<u></u>	100.00	<u> uM</u>	-68.520	

FIG. 3II SUBSTITUTE SHEET (RULE 28)

<u> </u>		74.05	T 14	7.450
		31.25		-7.450 111.670
		9.77		111.630
		3.05	IUM	64.340
· · · · · · · · · · · · · · · · · · ·		953.67		4.740 -19.270
		298.02 93.13	INM DM	-26.660
		29.10		
		9.09		-28.880
		2.84	INM OM	-42.180 -41.300
		0.80		-39.220
		0.00	ITIN	-39.220
59-0118 ⁰	313.36			
		100.00	uM	-67.170
		31.25		-56.580
		9.77		-58.060
		3.05		-55.720
		953.67		-48.200
		298.02	nΜ	-50.300
		93.13		-33.310
		29.10		-47.340
		9.09		-49.310
		2.84	nM	-56.200
		0.80	nM	-57.310
59-0119	314.34			
33 3.13	- 014.04	100.00	uM	167.500
""		31.25		-29.240
		9.77		-57.800
		3.05		-52.030
		953.67		-54.240
		298.02		-53.870
		93.13	nM	-38.110
		29.10	nM	-55.100
		9.09	nM	-52.270
		2.84	nM	-53.500
		0.80	nM	-43.650
O OH O OH				
59-0120	504.49			
	204.43	100.00	uM	-82.790
		31.25		-80.470
		9.77		-66.800
		3.05	uM Mu	-50.790
		953.67	nМ	-54.240
		298.02	nM	-45.250
		93.13	nM	-50.660

FIG. 3JJ SUBSTITUTE SHEET (RULE 28)

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29.10 lnM -50.300 9.09 lnM -50.300 2.84 lnM -50.300 0.80 lnM -43.280 100.00 lnM -79.690 31.25 lnM -75.590 9.77 lnM 25.650 9.30 lnM -4.150 9.31 lnM -4.150 298.02 lnM -1.800 9.09 lnM -22.050 9.09 lnM -22.050 9.09 lnM -26.760 0.80 lnM -28.270 100.00 lnM -28.270 100.00 lnM -28.270 100.00 lnM -31.110 100.00 lnM -31.110 100.00 lnM -31.110 100.00 lnM -31.110 100.00 lnM -31.110 100.00 lnM -31.110 100.00 lnM -31.110 100.00 lnM -31.110 100.00 lnM -31.110 100.00 lnM -31.110 100.00 lnM -31.110 100.00 lnM -31.200 100.00 lnM -30.200		T	20.10	Cit a	50,700	
2.84 nM					-50.300	
100.00 M		 	9.09	nM		
59-0121 245.29 100.00 uM						
100.00 luM			<u> </u>	пм	-43.280	
100.00 luM	CINT N					
100.00 luM	50 0:01 H	245 20				
31.25 UM	59-0121	243.23	100.00	M	-79 690	
9.77 luM 25.650 3.05 luM 94.850 953.67 lnM 43.910 298.02 lnM -1.800 93.13 lnM -2.050 29.10 lnM -22.050 9.09 lnM -31.110 2.84 lnM -26.760 0.80 lnM -28.270 NHH 31.25 luM -12.080 9.77 luM -7.610 3.05 luM 25.210 953.67 lnM 83.580 298.02 lnM 87.220 93.13 lnM 63.890 93.13 lnM 63.890 298.02 lnM 87.220 93.13 lnM 42.680 9.99 lnM 45.320 2.84 lnM 37.780 0.80 lnM 27.030 100.00 luM 34.430 31.25 luM 37.780 0.80 lnM 27.030 9.97 luM 38.620 3.05 luM 35.100 9.97 luM 38.620 3.05 luM 55.100 9.97 luM 38.620 3.05 luM 55.100 9.93.13 lnM 29.970 298.02 lnM 51.900 9.93.13 lnM 29.970 298.02 lnM 51.900 9.99 lnM 41.110	· · · · · · · · · · · · · · · · · · ·	+				
3.05 LM 94.850 953.67 nM 43.910 298.02 nM -1.800 93.13 nM -4.150 299.10 nM -22.050 9.09 nM -31.110 2.84 nM -26.760 0.80 nM -28.270 NH 59-0122 333.39 100.00 LM -19.050 9.77 LM -7.610 3.05 LM 25.210 9.77 LM -7.610 3.05 LM 83.580 9.77 LM 83.580 9.78 nM 83.580 9.79 nM 87.220 93.13 nM 63.890 9.99 nM 67.220 93.13 nM 63.890 100.00 LM 34.300 100.00 LM 37.780 100.00 L						
953.67 nM		+				
298.02 nM		 				
93.13 nM						_
29.10 nM -22.050 9.09 nM -31.110 2.84 nM -26.760 0.80 nM -28.270 100.00 uM -19.050 31.25 uM -12.080 9.77 uM -7.610 3.05 uM 25.210 953.67 nM 83.580 298.02 nM 87.220 93.13 nM 63.890 29.10 nM 42.680 9.09 nM 45.320 2.84 nM 37.780 0.80 nM 27.030 100.00 uM 34.430 33.125 uM 34.710 9.77 uM 38.620 3.05 uM 55.100 953.67 nM 51.900 953.67 nM 51.900 953.67 nM 51.900 953.67 nM 51.900 985.02 nM 41.410 93.13 nM 29.970 29.10 uM 13.760 9.09 nM 17.120						
9.09 nM -31.110 2.84 nM -26.760 0.80 nM -28.270						
2.84 nM -26.760 0.80 nM -28.270 59-0122 333.39 100.00 uM -19.050 31.25 uM -12.080 9.77 uM -7.610 3.05 uM 25.210 953.67 nM 83.580 298.02 nM 87.220 93.13 nM 63.890 29.10 nM 42.680 9.99 nM 45.320 2.84 nM 37.780 0.80 nM 27.030 100.00 uM 34.430 0.80 nM 27.030 59-0123 347.42 100.00 uM 34.430 0.80 nM 27.030 100.00 uM 34.430 0.80 nM 27.030 100.00 uM 34.430 0.80 nM 27.030 100.00 uM 34.430 0.80 nM 27.030 100.00 uM 34.430 0.80 nM 27.030 100.00 uM 34.430 0.80 nM 27.030		1				
59-0122 333.39 100.00 uM -19.050 31.25 uM -12.080 9.77 uM -7.610 3.05 uM 25.210 953.67 nM 83.580 93.13 nM 63.890 29.10 nM 42.680 9.09 nM 45.320 9.09 nM 45.320 2.84 nM 37.780 0.80 nM 27.030 9.08 nM 27.030 9.08 nM 27.030 9.09 nM 38.620 3.05 uM 55.100 9.09 nM 55.100 9.09 nM 55.100 9.09 nM 55.100 9.09 nM 51.900 298.02 nM 41.410 9.3.13 nM 29.970 29.10 uM 13.760 9.09 nM 17.120		 			-26.760	
59-0122 333.39 100.00 uM -19.050 31.25 uM -12.080 9.77 uM -7.610 3.05 uM 25.210 953.67 nM 83.580 298.02 nM 87.220 93.13 nM 63.890 29.10 nM 42.680 9.09 nM 45.320 2.84 nM 37.780 0.80 nM 27.030 59-0123 347.42 100.00 uM 34.430 37.780 0.80 nM 27.030 347.42 100.00 uM 34.430 37.780 0.80 nM 57.000 0.80 nM 57.000 0.80 nM 57.000 0.80 nM 57.000 0.80 nM 57.000 0.80 nM 57.000 0.80 nM 57.000 0.903 nM 57.000 0.903 nM 57.000 0.903 nM 57.000 0.903 nM 57.000 0.903 nM 29.970 0.900 nM 13.760 0.900 nM 13.760 0.900 nM 13.760 0.900 nM 17.120		1				
100.00 uM	N					
100.00 uM -19.050 31.25 uM -12.080 9.77 uM -7.610 3.05 uM 25.210 953.67 nM 83.580 298.02 nM 87.220 93.13 nM 63.890 29.10 nM 42.680 9.09 nM 45.320 2.84 nM 37.780 0.80 nM 27.030 100.00 uM 34.430 31.25 uM 34.710 9.77 uM 38.620 3.05 uM 55.100 953.67 nM 51.900 298.02 nM 51.900 298.02 nM 51.900 298.02 nM 41.410 93.13 nM 29.970 29.90 nM 13.7660 99.09 nM 13.7660	59-0192	333.39				
31.25 uM -12.080 9.77 uM -7.610 3.05 uM 25.210 953.67 nM 83.580 298.02 nM 87.220 93.13 nM 63.890 29.10 nM 42.680 9.09 nM 45.320 2.84 nM 37.780 0.80 nM 27.030 N 31.25 uM 34.430 31.25 uM 34.710 9.77 uM 38.620 3.05 uM 55.100 953.67 nM 51.900 298.02 nM 41.410 93.13 nM 29.970 29.90 nM 13.760 9.09 nM 13.760	05 0132	1	100.00	uM	-19.050	
9.77 uM						
3.05 uM 25.210 953.67 nM 83.580 298.02 nM 87.220 93.13 nM 63.890 29.10 nM 42.680 9.09 nM 45.320 2.84 nM 37.780 0.80 nM 27.030 100.00 uM 34.430 31.25 uM 34.710 9.77 uM 38.620 3.05 uM 55.100 953.67 nM 51.900 298.02 nM 41.410 93.13 nM 29.970 29.10 uM 13.760 9.09 nM 17.120						
953.67 nM 83.580 298.02 nM 87.220 93.13 nM 63.890 29.10 nM 42.680 9.09 nM 45.320 2.84 nM 37.780 0.80 nM 27.030 N 31.25 uM 34.710 9.77 uM 38.620 3.05 uM 55.100 953.67 nM 51.900 298.02 nM 41.410 93.13 nM 29.970 29.10 uM 13.760 9.09 nM 17.120			3.05	uM	25.210	
93.13 nM 63.890 29.10 nM 42.680 9.09 nM 45.320 2.84 nM 37.780 0.80 nM 27.030 100.00 uM 34.430 31.25 uM 34.710 9.77 uM 38.620 3.05 uM 55.100 953.67 nM 51.900 298.02 nM 41.410 93.13 nM 29.970 29.10 uM 13.760 9.09 nM 17.120			953.67	nM		
29.10 nM 42.680 9.09 nM 45.320 2.84 nM 37.780 0.80 nM 27.030 59-0123 347.42 100.00 uM 34.430 31.25 uM 34.710 9.77 uM 38.620 3.05 uM 55.100 953.67 nM 51.900 298.02 nM 41.410 93.13 nM 29.970 29.10 uM 13.760 9.09 nM 17.120						
9.09 nM 45.320 2.84 nM 37.780 0.80 nM 27.030 59-0123 347.42 100.00 uM 34.430 31.25 uM 34.710 9.77 uM 38.620 3.05 uM 55.100 953.67 nM 51.900 298.02 nM 41.410 93.13 nM 29.970 29.10 uM 13.760 9.09 nM 17.120					63.890	
2.84 nM 37.780 0.80 nM 27.030 59-0123 347.42 100.00 uM 34.430 31.25 uM 34.710 9.77 uM 38.620 3.05 uM 55.100 953.67 nM 51.900 298.02 nM 41.410 93.13 nM 29.970 29.10 uM 13.760 9.09 nM 17.120			29.10	nM		
0.80 nM 27.030 59-0123 347.42 100.00 uM 34.430 31.25 uM 34.710 9.77 uM 38.620 3.05 uM 55.100 953.67 nM 51.900 953.67 nM 51.900 298.02 nM 41.410 93.13 nM 29.970 29.10 uM 13.760 9.09 nM 17.120						
59-0123 347.42 100.00 uM						
59-0123 347.42 100.00 uM			0.80	nM.	27.030	
100.00 uM 34.430 31.25 uM 34.710 9.77 uM 38.620 3.05 uM 55.100 953.67 nM 51.900 298.02 nM 41.410 93.13 nM 29.970 29.10 uM 13.760 9.09 nM 17.120	N O TO N					
100.00 uM 34.430 31.25 uM 34.710 9.77 uM 38.620 3.05 uM 55.100 953.67 nM 51.900 298.02 nM 41.410 93.13 nM 29.970 29.10 uM 13.760 9.09 nM 17.120	59-0123	347.42				
31.25 uM 34.710 9.77 uM 38.620 3.05 uM 55.100 953.67 nM 51.900 298.02 nM 41.410 93.13 nM 29.970 29.10 uM 13.760 9.09 nM 17.120			100.00	uM	34,430	
9,77 uM 38.620 3.05 uM 55.100 953.67 nM 51.900 298.02 nM 41.410 93.13 nM 29.970 29.10 uM 13.760 9,09 nM 17.120						
3.05 uM 55.100 953.67 nM 51.900 298.02 nM 41.410 93.13 nM 29.970 29.10 uM 13.760 9.09 nM 17.120					38.620	
953.67 nM 51.900 298.02 nM 41.410 93.13 nM 29.970 29.10 uM 13.760 9.09 nM 17.120			3.05	uM	55.100	
93.13 nM 29.970 29.10 uM 13.760 9.09 nM 17.120			953.67	nM	51.900	
29.10 uM 13.760 9.09 nM 17.120					41.410	
9.09 nM 17.120	·	+				
) [2 84 int 1 33.480]						
0.80 lnM 1.190		 			13.480	

FIG. 3KK SUBSTITUTE SHIET (RULE 28)

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			ļ	1	
59-0124	350.44			·	
		100.00	uM	56.640	
-		31.25		81.500	
		9.77		145.880	
		3.05	uM	135.830	
		953.67		268.990	
		298.02		224.290	-
		93.13		134.850	
		29.10	nM	91.690	
		9.09	nM	80.390	
,		2.84	nM	63.060	
		0.80	nM	51.460	
N S N					
HO					
ОН	1			1 1	
59-0125	372.45				
		100.00	uM	-6.780	
		31.25		67.530	
		9.77		54.120	
		3.05		28.700	
		953.67		21.580	
		298.02	nM	22.280	
		93.13	nM	22.700	
		29.10		1.630	
		9.09		15.700	
		2.84	nM	9.840	
		0.80	nM	8.460	

FIG. 3LL

SUBSTITUTE SHEET (RULE 26)

					
N N					
	1				1
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Ó			1		l
59-0126	260.30		1		Ì
	200.50	100.00	I LIM	-17.390	
		31.25		-13.100	
		9.77	IuM	9.270	
	 	3.05	luM	40.530	
		953.67		21.390	
		298.02		25.660	
		93.13		9.430	
		29.10		6.360	
		9.09		6.510	
		2.84	nM	0.080	
		0.80		3.750	
			<u> </u>	550	
l , N					
NH			1		
l N			ŀ		
N_N					
) —(] .		
59-0127	329.41				
		100.00		-20.610	
		31.25		-21.820	
		9.77		-6.060	
		3.05		-3.900	
		953.67	nM	-8.820	
		298.02	InM	-6.200	
		93.13		11.880	
		29.10		1.610	
		9.09 2.84	nM nV	3.600	 .
		0.80		-2.070	
		0.80	[I IIVI	4.220	
	•		1		
0==<					
NH NH					
N CI			į		i
H ————————————————————————————————————					
59-0128 CI	470.74		ļ		
35-0120	436.34	100.00			
		100.00			
		31.25			
		9.77			
		3.05			
		953.67			
	 -	298.02			
		93.13 29.10			
		73,101	UMi		

FIG. 3MM SUBSTITUTE SHEET (RULE 20)

				,	, ··· .
ļ	 	9.09		<u> </u>	
	1	2.84		<u></u>	
	 	0.80	nM		
CI					
59-0129	077.7/				
35-0128	277.71	100.00	i i i	ļ <u>-</u>	
	 	100.00		-20.46	
	 	31.25		-21.21	
		9.77 3.05		44.36	
	 			4.38 5.9	
	 -	953.67 298.02		3.6	
	 	93.13	nM	2.07	
	 	29.10		4.22	
	 	9.09		-0.68	
	 	2.84	nM	12.48	
		0.80		-0.53	
		0.00		0.00	
41					
N N N N N N N N N N N N N N N N N N N					
, s <u> </u>		•			
59-0130	287.34				
		100.00	uM	4.38	
		31.25		8.35	
		9.77		5.91	
		3.05	иM	4.98	
		953.67	nM	0.39	
		298.02		8.66	
		93.13		2.85	
	ļ	29.10		3.6	
	ļ	9.09		4.36	
		2.84		8.96	
	 	0.80	nM	24.75	
				·	:
59-0131 ČI ČI	331.22	100.00			
		100.00		8.75	
,	 	31.25		0.12	
	 	9.77	uM 	-10.38	
		3.05 953.67	UM	-6.39	
		298.02	nM nM	-2.81 1.61	
		93.13	<u>um</u> nM	-1.98	
		29.10		-2.59	
		9.09	nM	0.14	
		2.84	Ma	0.14 -5.77	

FIG. 3NN SUBSTITUTE SHEET (RULE 29)

		0.80	nM	-0.5	
N NH O N O					
59-0132	313.32				
03 0102	313.32	100.00	liM.	-17.1	
		31.25		-14.81	
		9.77	uM	-14.37	
		3.05	uM	-12.92	
		953.67		-13.54	
		298.02	nM	-10.38	
		93.13		-3.65	
		29.10		-7.66	
		9.09	nM	-6.18	-
		2.84	nM	-9.97	
		0.80	nΜ	-2.81	
			. ,		r
59-0133	327.34	100.00	uМ	-16.04	
		31.25	иM	-16.91	
		9.77	иM	-17.31	
		3.05	uM	-16.7	
		953.67	nM	-9.34	
		298.02	nM	-12.69	
		93.13	nM	-11.23	
		29.10	nM	-17.74	
		9.09	nM	6.02	
		2.84	nМ	-4.71	
		0.80	nM	0.55	

FIG. 300 SUBSTITUTE SHEET (RULE 26)

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N. N.	1				
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			Ì		:
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0				;	
59-0134	357.37	_			
		100.00	Μш		
		31.25			
		9.77			
		3.05			
		953.67	nM		
		298.02	nM		
		93.13	nM .		
		29.10			
	<u> </u>	9.09	nM		
	ļ	2.84			
		0.80	nM		
\ <u>-</u>					
N NH		-			•]
0~N~0					
	1			•	ı
					Ī
	1				İ
]				
					[
59-0135	356.39				
		100.00	υM	-21.3	
		31.25		-14.16	
		9.77		-1.98	
		3.05		0.97	
		953.67	nM	11.68	
		298.02	nM	-1.13	
		93.13	nM	-1.55	
		29.10	nΜ	-2.81	
		9.09	nM	12.11	
		2.84	nM	-5.75	
		0.80	nM	4.54	
cı					
N OH					
59-0136	. 411 97			. l	
<u> </u>	411.87	100.00	uM		
	 -	100.00	MUM		
		31.25	M		
		9.77	WU		
		3.05	- MU		
		953.67	nM		

FIG. 3PP SUBSTITUTE SHEET (RULE 20)

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·					
		298.02	nM		
		93.13			
		29.10	nM		
		9.09	nM		
		2.84	nM		
	•	0.80	nM		
		:			
H HO					
59-0137	296.71		ļ <u> </u>		
		100.00	uM		
		31.25	uМ		
		9.77	uM		
		3.05	uМ		
		953.67	nM		
		298.02	nM		· · · · ·
		93.13	nM		
		29.10	InM		
		9.09	nM		
		2.84	nM		
		0.80			
		0.00	11160		
CIN CI			:		
0=<0-/					
59-0138	340.81				
		100.00	uM	-6.91	
		31.25	uM	-12.68	
		9.77	uM	4.59	
		3.05		32.61	
		953.67		19.07	
		298.02		8.18	
		93.13	nM	2.26	
		29.10		12.22	
		9.09		56.42	•
		2.84	nM	7.24	
		0.80		1.63	•
		3.00			
ON NO					
					·
59-0139	340.43				
	<u> </u>	100.00	JuM	45.53	
		31.25	uM .	44.59	
		9 <u>.77</u>	uM	53.62	
		3.05	Mu	30.42	
	1	953.67	InM	28.25	
į.			3 (1144		
		298.02 93.13	JuM	20.31	

FIG. 3QQ SUBSTITUTE SHEET (RULE 20)

		29.10	nM	14.4	
		9.09		13.93	
		2.84	nM	18.61	
		0.80		10.05	
		· · · · · · · · · · · · · · · · · · ·			·
CN CI					
CI CI	000 47	•		1	
59-0140	289.17	100.00		<u> </u>	
		31.25		 	
		9.77		 	
		3.05		 	
		953.67		 	
	-	298.02		 -	
		93.13		 	
		29.10		 	
		9.09		 - - - - - - - - 	
		2.84	nM		
		0.80			· · · · · · · · · · · · · · · · · · ·
N. a.					
l 🕜 á l					
59-0141	437.33				
		100.00		-6.76	
		31.25		5.69	
		9.77		19.85	
		3.05		43.96	
		953.67		44.73	
		298.02		37.12	
		93.13 29.10		24.36	
		9.09		26.7	
		2.84	nM n	15.96	
		0.80		7.87	
		0.00		7.87	
N COL	İ			1	
				1	
Cl Cl	į				
50.0440	772 00				
59-0142	379.29	400.05		 _	
		100.00		9.43	
		31.25	uM 	33.72	
		9.77		47.33	
		3.05	<u>um</u>	40.19	
		953.67	nM v	36.53	
		298.02 93.13	nw Mu	29.94	-
<u> </u>		93.13	H DAI	22.11	

FIG. 3RR Substitute sheet (rule 26)

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	T T	29.10	nM	20.9	
		9.09		19.14	
		2.84	nM	10.38	
		0.80		17.12	
CI CI					
59-0143 F F	447.29				
		100.00	1	0.4	
	<u> </u>	31.25		34.39	
		9.77		42.21	
		3.05		50.57	
	ļ	953.67		36.94	
		298.02	InM	27.23	
	 	93.13		16.99	
	 -	29.10 9.09		19.27	
		2.84		14.42	<i>'</i>
	 	0.80		23.72	
		0.60	TIM	23.72	
N N N H HO					
59-0144	316.40				
	<u>_</u>	100.00		-14.59	
		31.25		-4.44	
		9.77		47.1	
		3.05		53.89	
		953.67		43.11	
	 	298.02		29.2	
		93.13		18.5 12.9	
		29.10		5.54	
		9.09 2.84		3.71	
		0.80		5.87	
NH NH F		<u> </u>		5.57	
F NH					
59-0145	350.27				ļ
00 0110	330.27	100.00	uM	435.91	
		31.25		422.15	
		. 9.77		446.93	
		3.05	uM	434.17	
		953.67	nM_	238,34	
		298.02	lu <u>M</u>	45.99	
		93.13	nM	9,22	.]
		29.10	uM	7.71	
<u> </u>		9.09	lnM	0.11	

FIG. 3SS SUBSTITUTE SHEET (RULE 26)

		2.84	nM	6.27	
		0.80		3.55	
		0.00	TITIVI	3.33	
~ N					
				i	
59-0146	246.27			1	
00 0110	2.13.2	100.00	uМ	-63.05	
		31.25		4.42	
		9.77		-13.73	
		3.05		-16.45	
		953.67	nM	-35.47	
		298.02		-51.25	
		93.13	nM	-50.13	
		29.10	nM	-42.92	
		9.09		-45.64	
		2.84		-56.58	
		0.80	nM	-39.68	
TS-H-Q					
59-0147	314.36				
00 0117	011.00	100.00	пМ	-85	
		31.25		-85	
		9.77		-80.29	
		3.05		-41.67	
		953.67		78.69	
		298.02		269.13	
		93.13		323.59	
		29.10	nM	339.88	
		9.09	nM	270.48	
		2.84		245.58	
		0.80	nM	180.33	
The contraction of the contracti					
N J N					
59-0148	291.35]	
		100.00	иМ	-68.38	
		31,25		-36.33	
		9.77	uM	-2.3	
		3.05	uM	12.12	
		953.67	nM	-2.42	
		298.02	nM	-16.21	
		93.13	InM	-30.87	
		29.10 9.09	nM_	-35.58 -39.07	
<u> </u>		2.84		-39.07 -41.18	
		0.80		-45.53	
	l	<u>v.ov</u>	11 1141	10.00	

FIG. 3TT SUBSTITUTE SHEET (RULE 26)

				,	
0, /=\ /0					
				1 1	
S H O					
59-0149	329.33			1	
	<u> </u>	100.00	uM	-16.9	
,		31.25		-1.8	
		9.77		-0.53	
		3.05		15.29	
		953.67		78.78	
		298.02		163.5	
		93.13		223.57	
·		29.10	nM	173.93	
		9.09	nM	122.3	
		2.84	nM	98.02	
		0.80	лM	69.06	
	l T				
	1		l		
				1	
0 N					
59-0150	304.39				
		100.00	uМ	63.32	
		31.25		193.32	
		9.77		419.26	
		3.05		497.21	
74 - 24 - 4 - 4 - 4 - 4 - 4 - 4 - 4 - 4 -	·	953.67		295.19	
		298.02	nM	193.35	_
		93.13	nМ	99.46	
		29.10	nM	69.96	
		9.09	nM	59	
		2.84		52.16	
		0.80	nM	48.75	
	1]	
				1	
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]			1	
0 0				[]	
59-0151	278.311	,		[
59-0151		100.00	uM	-6.660	
		31.25		16.240	
		9.77	uM	18.300	
		3.05	uМ	11.690	
		953.67	nM	8.500	
		298.02	nM	9.070	
	 	93.13 29.10	nM	6.110	
		29.10	nM	5.880	
· · · · · · · · · · · · · · · · · · ·		9.09		7.700	
	 	2.84 0.80	nM	2.000	
L	<u> </u>	0.00	HM	1.7.0	

FIG. 3UU SUBSTITUTE SHEET (RULE 28)

	<u> </u>				
Н					
			}		
			1		
59-0152 O F	266.275				
59-0152		100.00	uM	-6.890	
		31.25		12.490	
		9.77		21.950	
		3.05		12.820	
		953.67		7.350	
		298.02	nM	4.290	· •
		93.13	nM	9.750	
		29.10	nM	4.860	
		9.09	nM	1.320	
		2.84	nМ	4.280	
		0.80	nM	4.160	
]	
				1	
o Ci					
59-0153	282.73			ļ .	
59-0153		100.00	uM	-4.150	,
		31.25		-0.390	
		9.77		11.120	
		3.05		14.540	
		953.67	nM	9.520	
		298.02	nM	11.570	
		93.13	nM	-0.160	
		29.10	nM	1.550	
		9.09		-0.960	
		2.84		4.730	
	 	0.80	nM	5.650	·=
	}				
	1			1	
N N N					
Ö					
				1	
59-0154	262.312				
59-0154		100.00		0,290	
		31.25		24.670	
		9.77	uM	15.680	
	 	3.05	uM	14.540	
		953.67	nM	13.170	
	 	298.02	nM	5.540	
	 	93.13 29.10	nM nM	2.690	
	 	9.09		-1.190 2.460	-
	 	2.84		4.170	
	 	0.80	nM	1.890	
<u> </u>	·	0.00		1.0001	

FIG. 3VV Substitute sheet (rule 26)

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0 F						
1	740 000			1		
59-0155	316.282		<u> </u>			
59-0155		100.00		-2.950		
		31.25		1.900		
		9.77	uМ	-9.450		
		3.05		-0.220		
<u></u>		953.67		0.690		
		298.02		5.090		
		93.13		-3.250		
			nM	0.530		
		9.09		-1.900		
		2.84 0.80	IDM	9.480		
		<u> </u>	INM	-1.130		
					·	
50 0156	333.391				İ	
59-0156 59-0156	300.031	100.00		F 040		
139-0130		100.00		5.840 2.050		
		31.25 9.77	uM uM	7.960		
		3.05		6.890		
			nM	-0.370		
		298.02		-1.880		
			nM	-3.550		
			nM	-7.340		
		9.09		-1.590		
			nM	2.650		
			nM	2.500		
59-0157	290.366		L			[
59-0157		100.00	иM	-6.440		
		31.25		14.920		
		9.77	uМ	19.930		
		3.05		11.440		
		953.67		8.570		
		298.02		-7.190]
		93.13		0.080		
		29.10		-0.230]
		9.09	Ma	-4.460		
		2.84	nM	2.200		
		0.80	nM	9.920		

FIG. 3WW SUBSTITUTE SHEET (RULE 26)

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Ĭ ,						
59-0158	308.337					
59-0158		100.00	uM	5.980		
		31.25		3.720		
		9.77		16.140		
		3.05		27.060		
			nM	9.930		-
		298.02		11.900		
		93.13	nΜ	2.810		
		29.10	nM	3.110		
		9.09		0.690		
		2.84		1.900		
		0.80	nM	7.970		
						ļ
H P			[
$N \sim N$						
			1			
59-0159	308.337					
59-0159		100.00	иМ	2.790		
		31.25		13.530		
			uM	4.700		
		3.05		10.910		
			nM.	2.800		
			nM	9.710		
			nM	4.830		
		29.10	nM	0.650		
		9.09	nM	5.900		
		2.84		6.610		
		0.80	nM	6.250		
59-0160	319.408					
59-0160		100.00	υМ	-5.060		
		31.25	uМ	-3.390		
		9.77	uМ	5.300		
		3.05		15.910		
		953.67		6.610		
		298.02		11.380		
		93.13		4.460		
		29.10		3.520		
		9.09		4.700		
		2.84	nM	-0.650		
		0.80	InM	7.560		

FIG. 3XX Substitute sheet (rule 26)

54/174

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S H CI						
	323.201					
59-0196 59-0196	525.201	100.00	uM	· ·-· ·	ļ ————	
39-0190	-	31.25		 	<u> </u>	
		9.77	uM	 		
		3.05		 	-	
		953.67	nM	1		
		298.02	DM			
		93.13	nM			
· · · · · · · · · · · · · · · · · · ·		29.10				
		9.09		_		
		2.84	nM	 		
		0.80	nM		<u> </u>	
O CI		0.00				
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CI			·			
S H			,			
59-0197	323.201					
59-0197		100.00	иМ			
		31.25				
		9.77				
		3.05	uM			
		953.67				
		298.02	nM			
		93.13				
		29.10				
		- 9.09				
		2.84	nM			
		0.80	nM			
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N N			 			İ
59-0198 59-0198	261.324				·	
59-0198		100.00	uM		•	
		31.25	uM	_		
		9.77	uМ			
		3.05	uМ			
		953.67	lnΜ			
		298.02 93.13	nM			
		93.13	nM			
		29.10	nM			
		9.09	nM			
		2.84 0.80	nM	ļ	<u> </u>	
		0.80	nM ·			
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59-0199	291.35		<u> </u>		·	
59-0199		100.00	luM			
		31.25	<u>luM</u>	<u> </u>	L	

FIG. 3YY SUBSTITUTE SHEET (RULE 20)

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	\mathbf{L}		J	/4

	<u> 55 / 17</u>	4				
		9.77	7 uM b uM			
		3.05	uM			
		953.67	'nM			
		298.02	nM			
		93,13	nM			
		29.10) nM		1	
		9.09	n M			
		2.84	inM		 	
		2.84 0.80	nM		 	
HOO	—	0.00	11.10		 	
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N''Y						[
59-0200 H	342.351					
59-0200 1 59-0200	0.2.001	100.00	luM		 	
00 0200	·	31.25			 	
		9.77	I LIM		 	
		3.05	Jum	<u> </u>	 	
		3.05	UM	 	 	ļ
		953.67	INM		ļ	
		298.02	INM.		<u> </u>	
		93.13	InM			
		29.10	InM			
		9.09	nM			
		2.84	lnM			
110 0		0.80	nM			
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H O			1 1			ļ i
<u>[59-0201]</u>	331.328		<u> </u>			i
59-0201		100.00	uM			
		31.25	uМ			
		9.77	uМ			
		3.05	uM			
		953.67	nM			
		298.02	nM			
	·	93.13				
		29.10	nM			
		9.09		•		
		2.84	nM			
		0.80	nM			
0, /=\		0.00	*****			<u> </u>
		:				
S' H un	1	٠.			!	
59-0202	300.336		}			
59-0202		100.00	uM			
		31.25	uM			
		9.77				
		3./ <u>/</u>	··M			
		3.05	uM			
		953.67	nM Mai			
		298.02	nM .			
		93.13	nm .			
L		29.10	nM			

FIG. 3ZZ SUBSTITUTE SHEET (RULE 20)

·						
		9.09	nM			
		2.84	nM			
		0.80	nM	T		<u> </u>
△ .N.						1
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▶ 人。/ Ⅰ	000 770		ļ	ì	i	
59-0203	292.338		<u> </u>	 		
59-0203		100.00				
		31.25				_
		9.77	uM			<u> </u>
		3.05	uM			
		953.67	nM			
		298.02	nM			
		93.13	nM			
		29.10				1
						
		9.09	inm	+		
		2.84	Inm			
		0.80	тим			
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Ŏ	744 700					
59-0204	344.389		<u> </u>			
59-0204		100.00		<u> </u>		
		31.25				
		9.77	7 uM			_
			uM			
		953.67	nM.			
		298.02				
	-		3 nM			
		29.10				
		9.0	9 nM			
		2.8	4 nM			
		0.8	0 nM			
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l s' ii a			1	- 1		
S H CI					1.	
59-0205	318.782	· ·				
59-0205		100.0	0 uM			
03 0200		71 2	5 uM			
	 	07	7 uM			
	 	3.7	7 um 5 uM			
	 	3.0	O IUM			
	 	953.6	/ INM			
	 	298.0	2 InM			
		93.1	3 nM			
		29.1	0 nM			
	1	9.0	9 nM			
	 	2.5	34 nM			
	 	0.5	30 nM			
	1	1	٠٠٠٠٠			

FIG. 3AAA SUBSTITUTE SHEET (RULE 26)

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N O					1	
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S' H		ļ	1		ł	
Cl' 7			1			1
59-0206	348.808	İ	1			
59-0206	340.000	100.00	 	 	——	ļ
05 0200		100.00			 	
	 	31.25	UM			<u> </u>
	 	9.77 3.05	UM	 -		
	 	953.67	Jum	- 	 	ļ
	 	298.02	INM	- 		
	 	93.13	InM			
	 	29.10		 	ļ.——	ļ
		9.09	ILIM	+	 	
	†	9.09 2.84	nM	 	 	
		0.80	nM	+	 	
○ N O		0.00	11141	 	 	
N O	[i				1	
N]					1
S H	1		1			
CI	1			Ì		
59-0207	348.808]	1		1
59-0207	340.000	100.00		 		
00 0207		100.00		 		
		31.25		ļ	ļ	
		9.77	им	 	ļ	
		3.05		 	 	
		953.67		 	ļ	
		298.02		<u> </u>		
		93.13		 		
		29.10				
		9.09	nM -M			
		2.84 0.80	nM nM	<u> </u>	ļ	
0		<u>U.6U</u>	I IIVI		 	
N 0						
I TINN TIL						
STH LOOF	•					
59-0208	338.307			[i		
59-0208		100.00	uM			
		31.25	uM	<u> </u>		
		9.77	uM			
		3.05	uM			
		953.67	nM			
		298.02	nM			
		93.13	nM			
		29.10	nM			
		9.09	nM			
		2.84	nM			
		0.80	nM			

FIG. 3BBB SUBSTITUTE SHEET (RULE 26)

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		1		<u> </u>	<u> </u>	
N N						ļ
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]
50 0000 OH	247.297					1
59-0209 OH 59-0209		100.00	uМ			
39-0209		31.25				
		9.77	иМ			
		3.05	uM			
		953.67	nM			
		298.02	nM			
		298.02 93.13	лM			
		29.10	nM			
		9.09	nM			ļ
		9.09 2.84 0.80	nМ			ļ
		0.80	nM	<u> </u>		
N,						
s' — Q						
<u> </u>						
59-0210	297.376					
59-0210		100.00	uM			
		31.25	иМ			<u> </u>
		9.77	uM			ļ
		3.05	uM			
		953.67	nM			ļ. <u> </u>
	· · ·	298.02	nM	ļ		<u> </u>
		93.13			 	<u> </u>
		29.10		ļ	 	
		9.09	lnM			
		2.84	nM		 	
		0.80	I MM	 	 	
0≫0H]		· ·			
	1					1
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O N						
50-8000 H	222.742					1
179-0000	298.342		 			<u> </u>
59-8000		100.00				-
		31.25	JuM	 	 	
		9.77				-
			i uM	 	 	
		953.67	InM	 	 	
	 	298.02	I DM	+	1	
	 	93.13	NAM	 		
	 	29.10	N DM	 	+	
	 	9.05	nM nM	+	+	
	-	0.00) nM	+	+	
	<u> </u>	1 0.00	ATTIME.	J	_1	

FIG. 3CCC SUBSTITUTE SHEET (RULE 28)

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	i	ĺ			1	1
	ļ		}		ł	1
59-8001	255.273					
59-8001		100.00) uM			
		31.25				
		9.77				
		3.05				
		953.67				
		298.02				1
		93.13	nM			
		29.10	nM			
		9.09	Mn			
		2.84	-InM			
0 000	<u> </u>	0.80	nM	<u> </u>		
0 ~ 0H						
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			İ		Į.	Ĭ
50, 8003 H OH	!		i			i
<u> </u>	302.286				1	
59-8002		100.00	uM			
		31.25	uM			
		9.77				
		3.05				
		953.67				
		298.02				
		93.13				
		29.10	nМ			
		9.09				
		2.84				
		0.80	nM			
O≯OH						
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	}				i i	
NH ₂						İ
N N						
53-8005	270.288				1 1	1
59-8003		100.00	uМ		\vdash	
		31.25	uM			
		9.77	uМ		 	
		3.05	uM			
		953,67	nM			
		298.02	nM			
		93.13	nM			
		29.10	nM			
		9.09	nM			
		2.84	nM			
		0.80	nM			

FIG. 3DDD SURSTITUTE SHEFT (RIH F 9A)

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Iro ago H	331.371					·
59-8004	331.371	100.00		 	·	
59-8004		100.00				
		31.25	UM			\vdash
		9.77		 		
		3.05	UM	ļ		
		953.67		<u> </u>		
		298.02		<u> </u>		
		93.13		ļ		<u> </u>
		29.10		ļ		<u> </u>
		9.09	nM	ļ		ļ
		2.84	nM	ļ		
		0.80	nM			
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"						<u> </u>
59-8005	299.326					
59-8005		100.00				<u> </u>
		31.25	uM			
: 		9.77	uM	<u> </u>		
		3.05	uM			
: :		953.67		<u> </u>		
		298.02	nM			<u> </u>
		93.13				
		29.10	nM			
		9.09	nM			
		2.84	nM			
		0.80				
0 ≫ 0H						
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59-8006	327.38					<u> </u>
59-8006		100.00	uM			
		31.25	uM			
		9.77	luM		}	
		3.05	uM		i	
		953.67	lnM			
		298.02	nM			
		93.13	lnM		<u> </u>	
:		29.10	nM			
		9 09	nM	T	<u> </u>	
		9.09 2.84 0.80	nМ		 	
		0.80	nM	 	 	
	L	0.00	1	<u> </u>	1	

FIG. 3EEE SUBSTITUTE SHEET (RULE 20)

						
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59-8007	297.354			<u>_i</u>	1	
59-8007		100.00	uM			
		31.25	uM			
		9.77	uM			
		3.05	uM			i
		953.67				
		298.02	nM		1	<u> </u>
		93.13	nM	1		
		29.10	nM	 	 	<u> </u>
		9.09		 		
		2.84	nM	 	 	
		0.80	nM	 	 	
O≫OH		0.00	11143	1	 	 -
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59-8008	261.299]	
59-8008 59-8008		100.00	ı M	 		
		31.25				
		9.77	M			
		3.05	uM M			
				}	 	
		953.67		 		
		298.02	nM		ļ	
<u> </u>		93.13				
		29.10				
		9.09	nM			
		2.84	nM			
		0.80	nM	<u></u>		
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59-8009 N	289.313		i		i	
59-8009	203.313	100.00		 		
03 0003		100.00 31.25 9.77 3.05 953.67 298.02	UM		 	
 		<u> 51.25</u>	<u>uM</u>		ļ	
		9.77	uM	<u> </u>		}
		3.05	uM		<u> </u>	
		953.67	nM			
		298.02	nM			
<u> </u>			DW			
		29.10	nM			
		9.09	nM			
	<u></u>	2,031	1111	' 	<u></u>	

FIG. 3FFF SUBSTITUTE SHEET (RULE 26)

62 / 174

		0.04	1	Т	1	T
,		2.84 0.80	INM	 	 	
	-	0.80	INM		 	
O≫OH				1	Ì	}
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	1			1	į	
					1	•
NA FE						ŀ
H ~~~	004.000			İ	İ	
59-8010''	261.299			ļ	<u> </u>	[
59-8010	ļ	100.00	IUM			
	<u> </u>	31.25	luM .	 	ļ	ļ
	ļ	9.77	uM	 		ļ
		3.05	uM	<u> </u>	<u> </u>	<u></u>
		<u>953.67</u>	nM		ļ	<u> </u>
		298.02	nM		 	
• •		93.13	nM		<u> </u>	
		29.10	nM			
		9.09	nM	<u> </u>	ļ	
		2.84 0.80	nM			
		0.80	nM			
0 ≫ 0H				ļ		
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			<u> </u>			
N A		•		ļ		
)	İ		
59-8011	285.299			ł		
59-8011 59-8011		100.00	uM			
		31.25	иM	 		
· · · · · · · · · · · · · · · · · · ·		9.77	IuM			
		3.05	uM	 	<u> </u>	
·		953.67	D.M.	 		
		298.02	nM	1		
	 	93.13	nM	 		
		29.10	m k 4	 		
<u> </u>						
		23.10	11IVI:		 	
		9.09	nM.			
		9.09 2.84	nM nM			
		9.09	nM nM			
0 > 0H		9.09 2.84	nM nM			
ОТОН		9.09 2.84	nM nM			
		9.09 2.84	nM nM			
		9.09 2.84	nM nM			
O HO		9.09 2.84	nM nM			
		9.09 2.84	nM nM			
O HO		9.09 2.84	nM nM			
0 HO N S OH 59-8012	294.285	9.09 2.84	nM nM			
O HO	294.285	9.09 2.84 0.80	nM nM nM			
0 HO N S OH 59-8012	294.285	9.09 2.84 0.80	nM nM nM			
0 HO N S OH 59-8012	294.285	9,09 2.84 0.80 100.00 31.25	nM nM nM			
0 HO N S OH 59-8012	294.285	9,09 2.84 0.80 100.00 31.25 9.77	nM nM nM			
0 HO N S OH 59-8012	294.285	9,09 2.84 0.80 100.00 31.25	nM nM nM uM uM			

FIG. 3GGG SUBSTITUTE SHEET (RULE 26)

			,			
		93.13	nM			
		29.10	nM			
		9,09 2.84 0.80	nM			
		2.84	nM			
		0.80	nM	<u> </u>		
0 > ОН				1		
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	i		J			
			İ	1		
1 ~ ~ ~						1
F0 8017 H	701 704			i	1	l
139-8013	301.364				<u> </u>	<u> </u>
59-8013		100.00		-		ļ
		31.25	uM		<u> </u>	<u> </u>
		9.77	uM	<u> </u>		
		3.05	uM			
<u> </u>		953.67	nM	 	ļ	
		298.02	InM_	 -	<u> </u>	
<u> </u>		93.13		 	L	
		29.10		<u> </u>		
		9.09	nM			
		2.84	nM	<u> </u>		
		0.80	nM	<u> </u>		
0 ≫ 0H	j					1
	i					1
	1					İ
					i	
N-0						j
	1				1	Į
0	777 700					1
59-8014	377.396					
59-8014		100.00				
·		31.25	uM	<u> </u>		
		9.77	uM_	<u> </u>	<u></u>	
		3.05	uM_	<u> </u>		
		953.67	nM			
		298.02	nM			
		93.13	nM			
		29.10		ļ		
		9.09	nМ			
		2.84 0.80	nM			
		0.80	nM			
0 ⇒ 0H						
1 7	i					[
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NA C	i			1		! i
]	
F	ľ					
59-8015	285.299	1		}]	
59-8015		100.00	иM		 	 -
		31.25	ııM	 	 	
		9.77	uM	 		
		3.05	uM			<u> </u>
		J.UJ1	G (V)	<u> </u>	l	L

FIG. 3HHH Substitute sheet (rule 26)

		953.67	nM			
		298.02	nM			
		93.13	nM			1
		29.10				
		9.09				
		2.84	nM	<u> </u>		
		0.80	nM			
0						
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<u> </u>				ĺ	1	- "
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\sim N- \sim \sim \sim \sim			ļ			ļ
H			•			
0-					1	
59-8016	285.299					
59-8016		100.00	uM		<u> </u>	
		31.25	luM		İ	
, u/ = -		9.77	иM			
		3.05	uМ	-		
3 7 3 3		953.67				
		298.02	nM			
		93.13	nM			
-		29.10		<u> </u>		
		9.09			· · · · · · · · · · · · · · · · · · ·	1
		2.84	nM	 		
		0.80	nM	 		
		0.00	,,,,,,	 	· · · · · · · · · · · · · · · · · · ·	ļ
			 		 – –	
	·			 		
				 	· · · · · · · · · · · · · · · · · · ·	
	<u> </u>		<u> </u>	<u> </u>	L	L

FIG. 3III

SUBSTITUTE SHEET (RULE 26)

ABA-S

CHEMISTRY	CONCENTRATION	
N——OH		
51-2229		
51-2229	100.00	υM
	10.00	
210.236	2.00	
	0.40	
1	0.08	Ш
0		
		ŀ
000		
1 1		
92-3052		
92-3052	131.056	иM
	13.106	
381.516	2.621	
	0.524	
	0.105	
l o l		}
) \(\) \(\)		- 1
92-3390		
92-3390 92-3390	145.012	ıМ
	14.501	
344.798	2.900	\dashv
	0.580	\dashv
	0.116	\dashv
	30	\dashv
OH OH		
OH OH		
s o		
	i	
	ļ	
92-3552 92-3552		
92-3552	214.326	Mu

ı	 <u>'</u>	<u> </u>		
	12	20.		00000
		-9 113 12 20 24	9.2 3.8 2.6 9.2 1.4	80155
	 1	31 39	.05 .57 .68 .82	
	 10		.15	

FIG. 4A SUBSTITUTE SHEET (RULE 20)

	24 477	
677.000	21.433	<u> </u>
233.289	4.287	<u> </u>
<u> </u>	0.857	<u> </u>
	0.171	
F CI O CI		
92-6353		
92-6353	155.199	иМ
	31.040	
322.166	15.520	
322.100	3.104	
	1.552	-
	0.310	-
	0.510	
92-8007		
92-8007	181.613	ιΜ
32.0007	36.323	3.00
275.311	18.161	\vdash
273.511	3.632	-
	1.816	
	0.363	-
	0.363	
O CI		
92-8215		
92-8215	165.123	υМ
	33.025	†
302.805	16 512	
302.003	16.512 3.302	-
	1.651	├
	0.330	\vdash
	<u> </u>	1

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69.74	.]
74.50	7
31.59	_
39,70 18.29	
18.29	1
10.29	4
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204.14	
154.94	1
00.07	4
28.09	
	1
3.53	7
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- 16.65	١
50.55	7
58.65 142.33	4
142.33	
45,65	
45,05	4
4.47	1
****	i
32.90	-
1 12 90	١
52.50	_
151.06	_
151.06	_
151.06 132.29	
151.06 132.29 59.90	
151.06 132.29	
151.06 132.29	

FIG. 4B SUBSTITUTE SHEET (RULE 26)

T NH NH			
92-8258			
92-8258	162.102	иM	-16.65
	32.420		157.44
308.447	16.210		101.04
	3.242		39.02
	1.621		
	0.324		12.78
1~ #			
F _F			
0 NH F			
92-8362			
92-8362	154.647	uМ	136.79
	30.929		137.00
323.318	15.465		65.02
	3.093		17.34
	1.546		
	0.309		0.41
1			
Br			
			<u>, </u>
			,
H H			<u> </u>
92-8372			
92-8372	150.045	υМ	63.76
	30.009		134.71
333.234	15.004		92.06
	3.001		31.35
	1.500		
	0.300		13.20
0,			
) ──?			
N N			
$\int \int \int \int \int \int \int \int \int \int $,
0			
92-9183			
[JZ_ J10J			L

FIG. 4C SUBSTITUTE SHEET (MHE 2A)

92-9183	137.568	υМ
	13.757	
363.457	2.751	
	1.376	
	0.550	
	0.110	
OH		
I OH N I		
0	.	
93-0215		
93-0215	182.957	uМ
	18.296	
273.288	3.659	
	0.732	
	0.146	
N=<		
H-N-O CCI	·	
N N-P		
020	·	.
i ci		
93-0399		
93-0399	131.491	uМ
	13.149	
380.253	2.630	
	0.526	
-	0.105	
1		Ì
·		
	·	
		•
07 0697		
93-0587 93-0587	222 057	
33-036/	222.953 22.295	uМ
224.267	77.732	
224.263	4.459 0.892	
	0.178	
N TH	<i>:</i>	
~~ s' ~~) ~ o		
		Ì
		I
93-1327		
93-1327	119.764	
30 1027		uM
417.487	11.976	\dashv
417.487	2.395 0.479	\dashv
•	0.4/9	I

-22.80 16.61 101.96 58.17 38.47
115.230 88.110 20.870 -28.680 5.250
128.130 38.560 41.240 -4.910 3.910
178.130 60.410 -0.180 -3.470 -8.460
-42.000 119.130 67.930 8.520

FIG. 4D SUBSTITUTE SHEET (NULE 26)

14.870

	0.096
H 😅	
93-1340	
93-1340 93-1340	196.576 uM
	19.658
254.355	3.932
	0.786
	0.157
Cı	
_N 0	
N S N Br	
~ Br	
93-1474	
93-1474 93-1474	145.940 uM
	14.594
342.607	2.919
	0.584 0.117
	- 0.117
0,	
\ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \	
	j
	1
93-1766	•
93-1766	144.348 uM
	14.435
346.366	2.887
	0.577
	0.115
F./_	
H ₂ N _N F	
N NH-{_}	
N N	
1 - 1	
H H	
93-1866	·
93-1866	148.214 uM 14.821
	14.821

-31.290 127.340 35.710 37.630 7.280	
-45.110 110.290 35.080 109.040 40.130	
75.940 173.150	

FIG. 4E SUBSTITUTE SHEET (RULE 28)

850-7377 850-7377 131.062 uM 13.106 381.498 2.621 0.524 0.105 850-7413 111.964 uM 11.196 446.572 2.239 0.448 0.090
850-7377 850-7377 131.062 uM 13.106 381.498 2.621 0.524 0.105 HN 850-7413 111.964 uM 11.196 446.572 2.239 0.448 0.090
850-7377 850-7377 131.062 uM 13.106 381.498 2.621 0.524 0.105 HN 850-7413 111.964 uM 11.196 446.572 2.239 0.448 0.090
850-7377 850-7377 131.062 uM 13.106 381.498 2.621 0.524 0.105 HN 850-7413 111.964 uM 11.196 446.572 2.239 0.448 0.090
850-7377 850-7377 131.062 uM 13.106 381.498 2.621 0.524 0.105 850-7413 111.964 uM 11.196 446.572 2.239 0.448 0.090
850-7377 850-7377 131.062 uM 13.106 381.498 2.621 0.524 0.105 HN 850-7413 111.964 uM 11.196 446.572 2.239 0.448 0.090
850-7377 850-7377 131.062 uM 13.106 381.498 2.621 0.524 0.105 850-7413 111.964 uM 11.196 446.572 2.239 0.448 0.090
850-7413 850-7413 850-7413 111.964 JM 11.196 446.572 2.239 0.448 0.090
850-7413 850-7413 850-7413 111.964 JM 11.196 446.572 2.239 0.448 0.090
381.498 2.621 0.524 0.105 850-7413 850-7413 111.964 µM 11.196 446.572 2.239 0.448 0.090
850-7413 850-7413 850-7413 111.964 uM 11.196 446.572 2.239 0.448 0.090
850-7413 850-7413 111.964 µM 11.196 446.572 2.239 0.448 0.090
850-7413 850-7413 111.964 µM 11.196 446.572 2.239 0.448 0.090
850-7413 850-7413 111.964 µM 11.196 446.572 2.239 0.448 0.090
850-7413 850-7413 111.964 µM 11.196 446.572 2.239 0.448 0.090
850-7413 850-7413 111.964 uM 11.196 446.572 2.239 0.448 0.090
850-7413 850-7413 111.964 uM 11.196 446.572 2.239 0.448 0.090
850-7413 850-7413 111.964 uM 11.196 446.572 2.239 0.448 0.090
11.196 446.572 2.239 0.448 0.090
11.196 446.572 2.239 0.448 0.090
11.196 446.572 2.239 0.448 0.090
11.196 446.572 2.239 0.448 0.090
11.196 446.572 2.239 0.448 0.090
11.196 446.572 2.239 0.448 0.090
446.572 2.239 0.448 0.090
0.448 0.090
0.090 HO N-/
HO N-/
HO OH NHO NHO NHO S=0
OH NHO NHO NHO NHO NHO NHO NHO NHO NHO N
H H H N N N N N N N N N N N N N N N N N
H-17-17-18-0
0H 0
850-7449
850-7449 69.938 uM
1 6.994
714.923 1.399
714.923 1.399 0.280

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	61 25	.86	
	- 40	.44	
		.55	4
	157	.01 .73	+
	23	.91	٦
v			
	- 47	.42	,
	73	3.79	
	112	2.16	
	75	5.24 5.36	
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FIG. 4F SUBSTITUTE SHEET (RULE 28)

N ₂ O		
V 4 1 NH		
l s		
07 7485		
93-7485 93-7485	143.099	
90-7460	14.310	UM
349.409	2.862	H
545.466	0.572	H
	0.114	\vdash
	0.117	Н
N 1		
√ NH		
03_7001		
93-7991 93-7991	127.367	пМ
30 7301	12.737	
392.585	2.547	
	0.509	П
	0.102	
1		
HNTILO		
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N N		
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)		
1050 0470		
850-8170 850-8170	401 547	
050-01/0	101.513 10.151	uM
492.55	2.030	H
492.55	0.406	\vdash
	0.408	\vdash
L	1 0.061	

 -42	.91
28 153 74 50	.36 .04 .27 .28
-16 8 105 47 54	95
-33. 158. 126. 43. 50.	27

FIG. 4G

SUBSTITUTE SHEET (RULE 20)

72	/174	
م آه		
H N		
N		
850-8205 850-8205		
850-8205	104.478 10.448	uМ
478.57	2.090	
	0.418	
CHIRAL	0.084	
s		
, N		
NH		
0 0		
2 200		ŀ
Jon.		
850-8241 850-8241	82.279	иM
	8.226	
607.685	1.646 0.329	
	0.066	\vdash
T\$ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\	•	
N N N N N N N N N N N N N N N N N N N		
850-8278 850-8278	139.101	иМ
	13.910	
359.451	2.782 0.556	\vdash
	0.111	
H_0		
	. ,	
850-8367		

-39.52 51.18 163.82 106.06 73.68	
-2.07 181,77 118.23 66.73 36,14	
-40.09 39.00 182.38 122.84 78.90	
-	

FIG. 4H SUBSTITUTE SHEET (RULE 26)

050 9707	100 7001	
850-8387	122.392 ι	
100.503	12.239	130.3
408.523	2.448	129.75
	0.490	62.69
	0.098	40.74
HO HN OH		
850-8459 850-8459	87.921 u 8.792	M −21.13 11.30
568.692	1.758	131.92
000.002	0.352	71.13
	0.070	58.55
	0.070	
850-8613		
850-8613	151.319 u	M -26.05
	15.132	85.55
330.428	3.026	381.37
	0.605	255.32
	0.121	122.93
S H O O S O H		
850-8637	ļ	
850-8637	05 5101	d 05.43
3007	85.518 u 8.552	
F04 077	1 710	33.35
584.673	1.710	122.49 57.19
	0.342	5/.19
	0.068	37.42

FIG. 4I SUBSTITUTE SHEFT MHF 201

0 _{N=0}		
,		
	}	
N	İ	
N 0 un =0	1	
HN']	
()		
3/		
850-8889	1	
850-8889	111.493 uh	1 -17.470
000-0009	11.149	142.970
448.457	2.230	74.150
440,407	0.446	21.010
	0.089	8.530
	0.003	- 0.550
` '		
<i>)</i>		
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S CI	· 1	
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, jv-40	1	
H O 850-8964		
850-8964	95.156 ul	√l −30.92
	9.516	44.99
525.454	1.903	126.29
	0.381	49.84
	0.076	44.99
1		
N N		
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HÝ, €0		
S(~)	1	
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050 0074	· •	
850-9071 850-9071	. 109.998 ul	M -24.620
000-30/1	11.000	84.120
454 550	2 200	149.030
454.552	2.200 0.440	54.540
	0.440	34.340

FIG. 4J SUBSTITUTE SHEET (RULE 26)

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	0.088	23.540
,, Ó.,		
N II		
S		
N N S		
HN-_C		
850-9106 CI		
850-9106	100.000 uM	-15.710
	10.000	99.820
499.999	2.000	111.960
	0.400	74.500
	0.080	23.150
N = N = N = N = N = N = N = N = N = N =		
N N S		
850-9142 850-9142	0F F00 11	44.000
1000-3144	85.596 uM 8.560	-14.980 165.770
584.138	1.712	66.650
	0.342	27.780
	0.068	0.670
N →		
	1 1	
0 0 5		
N N	ii	
0 1		
850-9179 850-9179	105 757 11	04.670
1650-9179	105.357 uM 10.536	-24.630 105.200
474.579	2.107	89.280
	0.421	46.110
	0.064	19.160
H (ļ
N N		
_ s. []		
но		
nu l		
850-9212		
850-9212	92.139 uM	-26.580
F (0.053	9.214	40.900
542.657	1.843 0.369	111.690 76.950
	0.074	30.840
	3.577	

FIG. 4K SUBSTITUTE SHEET (RULE 26)

CI H O F F F F 850-9287		
850-9287		uМ
770 7	14.717	<u> </u>
339.744	2.943	
	0.589	
	0.118	<u> </u>
HO HO		
850-9356 850-9356	99.506	uМ
	9.951	CIAI
502.482	1.990	
	0.396	
	0.080	
HO OH OH		
850-9467		
850-9467	120.646	uM
44	12.065	_
414.436	2.413	
	0.483	ᆜ
	0.097	

15 130 91	.82 .82 .71 .11
-24.6 83.1 168.8 45.4 9,7	
-19.8 112.9 122.7 43.5 33.1	300 190 130 120 40

FIG. 4L SUBSTITUTE SHEET (RULE 26)

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NH 10 HN 350-9576	
NH TO HN S	
HN	
HN	
350-9576	
350-9576	
350-9576	
350-9576	
350-9576	
331U · 1	
350-9576 \\ 350-9576 \\ 111.724 \u	ıМ
11.172	<u> </u>
447.532 2.234	
0.447	
0.089	
	,
0 0 CI	
	i
Ö ci	
395-0262 395-0262 166.019 u	
	ML
33.204 301.169 16.602	-
301.169 16.602 3.320	_
0.332	
_	
,0	
A 14 1/	
395-0268	
395-0268 128.383 u	ıΜ
395-0268 128.383 u 25.677	Mı
395-0268 128.383 u	Mı

-27.430 90.560 101.610 44.900 19.930
-19.18 -12.60 148.28 -2.23 -3.07
-18.87 40.25 169.96 195.29 14.02

FIG. 4M **SUBSTITUTE SHEET (RULE 26)**

S	İ		
	}		
N			
895-0594			
895-0594	120.896	uM	-21.63
	12.090		25.89
413.58	2.418		122.10
	0.484		75.32
	0.097	 	39.42
S ,			
N			1
h 0 0			
895-0857			
895-0857	159.026	uM	-30.46
	15,903		146.74
314.407	3.181		74.54
· · · · · · · · · · · · · · · · · · ·	0.636		25.82
	0.127		3.66
,0-			
			1
		j	
N		ı	
895-0964			
895-0964	162,655	<u>uM</u>	-31.06
307.393	16.265	<u> </u>	325.06 87.51
507.353	3.253 0.651	 	40.30
	0.130		40.39 16.03
			10.00

FIG. 4N SUBSTITUTE SHEET (RULE 26)

		
Cl	:	1
H ₂ N CI		
NH ₂		
CI TY TY		
- "		
895-1161 895-1161	150 005	
895-1161	152.625	им
327.602	15.263	
327.802	3.053 0.611	\dashv
	0.122	\dashv
	0.122	\neg
		i
895-1420 N-N		
895-1420	220.965	uМ
	22.097	\exists
226.279	4.419	
	0.884	
	0.177	
N		
N-V		
n)		
9051670		1
895-1679 '	180.910	uМ
	18.091	
276.383	3.618	
	0.724	
	0.145	Ш
N-N-N		
1 !! %, ~		
H N OH		
895-1691		
895-1691	182.992	uМ
	18.292	├
273.34	3.658	$ldsymbol{ldsymbol{ldsymbol{eta}}}$

- 5.51 109.31 56.06 29.49 24.71	
-19.47 110.90 49.94 33.65 20.06	
-30,36 111,72 102,83 18,01 0,44	
-16.29 50.84 105.70	

FIG. 40 SUBSTITUTE SHEET (RULE 20)

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	<u></u>		
	0.7	32	60.23
	0.1		23.42
\sim			1
N. N			
M-M 15			
H N			
/			i 1
895-1754] {	
895-1754	104 2	95 uM	-31.44
090-1704	19.4		132.78
01		30	75.70
	7.341 3.8		75.39
	0.7		39.30
	0.1	55	16.19
A 11			
			1
	1]	1
			1
895-1888			
895-1888		04 uM	-33.65
	21.2		29.75
2	35.286 4.2	250	148.84
	0.8	350	73.77
		70	28.14
			20,14
į	İ		
		1 1	1 1
	į	1 1	1
	,		1
N-N		1 1	1
N-N'	1		
	1		
895-2474			
895-2474	184 (952 uM	-20.74
030 2777	18.4		128.69
		699	66.37
			43.27
		740	
	0.1	148	19.44
) , OH		1	
I NO		1 1	
			1
		1 1	
			.
805-2475	į		
895-2475	160	159 uM	265.41
895-2475	102.	139 UM	
		216	287.86
3	08.337 3.	243	227.34
		649	65.40
	0.	130	28.96

FIG. 4P SUBSTITUTE SHEET (RULE 28)

]
N-OH]
895-2544		1
895-2544	190 190	
	189.186 uM	4
264.284	18.919	136.50
204.204		59.15
	0.757	24.75
	0.151	11.86
}_		
<u>895–3113</u> 0]	
895-3113	160.067 uM	
	16.007 Jun	-22.22
312.372		224.52
312.372		68.46
	0.640	43.36
	0.128	30,56
		·
\ \ \ \ \	1 1	
N V		
\ '\\]]	
POS 7700		
895-3306	<u> </u>	·
895-3306	172.170 uM	-23.24
	17.217	38.63
290.41	3.443	333.10
	0.689	164.63
	0.136	64.33
	900	- 04.33
_ H_0		
N~0		
\∕ NN		
HN'. /		
PAG 701A		l
895-3810 805-3810		1
895-3810	196.973 uM	89.79
	19.897	106.75
251.289	3.979	73.78
	0.796	73.78 33.45
	0.159	16.86
		10.00

FIG. 4Q SUBSTITUTE SHEET (RULE 26)

N N H		·			
895-7985					
895-7985		223.935	ML		122.070
		22.394			3.900
	223.279	4.479	\neg		-7.790
		0.896	\dashv		5.520
		0.179	\dashv		-2.270
S N					
1 0, 0,			- 1		1
895-7997			- 1		
895-7997		176.461	иМ	i	
		17.646			
	283.349	3.529			
		0.706			
		0.141	\neg		
Br NH H					·
895-8053				•	
895-8053		134.398	uМ		
		13.440			
	372.03	2.666			
		0.538			
		0.108			
HO OH OH OH					
895-8137					
895-8137		169.326	uM		

FIG. 4T SUBSTITUTE SHEET (RULE 20)

	16.933	TT	ſ	·
295.288	3.387	TT	ı	
	0.677		T I	
	0.135		1	
			Ī	
			i	
		[]	
			}	
0		1 1	}	
0-			1	
005 0405				
895-8185			1	
895-8185	219.057	uМ	<u> </u>	
	21.906			
228.251	4.361			
	0.876	\neg	<u> </u>	
	0.175			
Br		_	-	
N L 0				
, N		i	i	
H NH-N	ļ			
895-8286				
895-8286			L	
0.00 0.00	142.765	<u>uM</u>		142.210
750 000	14.277		L	40.390
350.225	2.855			17.850
	0.571			-10.890
	0.114			6.580
			-	
Q H CI				
			1	
/ N				
	1		İ	
	1		l	
895-8383	j			
895-8383		_	L.	
000 0000	191.774 u	M		-44.020
	19.177	_]		76.480
260.724	3.835	_]		135.940
	0.767	_]		77.030
	0.153			37.630
			<u> </u>	

FIG. 4U SUBSTITUTE SHEET (RULE 26)

895-8862 895-8862 301.43	165.876 16.588 3.318 0.664	uM
	0.133	$\vdash \vdash \vdash$
	0.133	Ш
CI NH NH 805-9683		
895-9683 895-9683	113.552	υM
093-9063	11.355	3111
140 726		-
440.326	2.271	-
	0.454	\vdash
	0.091	 :
N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-		
895-9896		1
895-9896	178.349	uМ
	17.835	
280.349	3.567	П
	0.713	
	0.143	T
	U. 1-7-U	<u></u> -

	54.72 159.21 113.97 41.96 38.28
•	-20.67 201.56 12.55 0.62 -0.69
	-29.16 0.62 182.84 118.55 42.75

FIG. 4V
SUBSTITUTE SHEET (RULE 26)

	OIL			
	H N-N			
896-0122	H N-N H			
896-0122			190.610 uM	-14.15
			19.061	151.42
		262.316	3.812	56.90
			0.762 0.152	19.20 11.42
				, , , , , , , ,
	S, H CI			
896-0246 896-0246				
090-0246			154.888 uM 15.489	-17.57
		322.814	3.096	34.35 102.03
			0.620	46.52
			0.124	20.52
	o. H			
	H			
	S			
	-0			
896-0255 896-0255	\\			
090-0233			123.000 uM 12.300	-17.14
		406.504	2.480	67.75 168.78
			0.492	61.27
			0.098	49.97
	NH	<u> </u>		
	0	/		
	N'N Y N			
	NH H			
			.]]	
	Cl			
396-0345				
396-0345			107.532 uM	-18.86
			10.753	77.80
			_	

FIG. 4W SUBSTITUTE SHEET (RULE 28)

464.979	2.151	
	0.430	
	0.086	
/=\		
N N	ŀ	
HN S'		
	·	
	ŀ	
	,	
896-0390	100 710	
896-0390	128.718 u	ML
700 445	12.872	
388.445	2.574	
	0.515	
	0.103	
<u> </u>		
, O H		
	ł	
H		
N N		
5		
	1	
896-0535		
896-0535	132.810	ıΜ
	13.281	
376.478	2.656	
	0.531	
	0.106	
⟨ _∕rs		
HUNICI		
l A M	[[
896-0554	<u> </u>	
896-0554	121.499	иM
	12.150	
411.527	2.430	
	0.486	
	0.097	

188.94 106.12 37.18	
-16.90 87.23 210.25 73.35 28.25	
- 10.41 73.84 199.80 102.12 35.72	
-16.32 105.48 115.43 53.88 27.03	

FIG. 4X

CI—()—()	i	
O HN		
896-0686 896-0686		
030 0000	191.774 uM	-19.80
260.72	19.177	176.04
200.72	4 3.835 0.767	115.02
U	0.767	97.67
0 N	0.133	25.27
CI H		
I N]
S		
		1 1
896-0692		
896-0692	171 000	
	131.269 uM	22.78
380.897	13.127	149.23
	0.525	78.33
	0.105	51.06 46.12
0. H	5.100	40.12
1 VA		
-		
N N		
S		
\ \ \		
NH ²		
896-0719		
896-0719	91.950 uM	
	9.195	-6.49
543.774	1.839	187.43
	1.839 0.366	127.43 50.04
	0.074	36.16
		30.10
O CI		
CI N CI		
896-0773		
896-0773	147.228 uM	-13 04
	14.723	-13.94 175.33
339.609	2.945	221.91
	0.589	221.91 52.48
	0.118	32.99
	_	

FIG. 4Y SUBSTITUTE SHEET (RULE 20)

	_		
NH S NH			
896-0819		101010	
896-0819		124.219	uМ
	400 540	12.422	Щ
	402.516	2.484	$\vdash \vdash$
		0.497	\vdash
		0.099	\dashv
NH 0 NH 0 NH 0 NH 0 NH 0 NH 0			
896-0853		157.546	иМ
		15.755	
	317.367	3.151	
		0.630	
		0.126	
S NH O			
896-0921	1		
896-0921		174.583	uМ
		17.458	
	266.397	3.492	П
		0.698	
		0.140	
		0,,,,	

-16.20	
70.03	
70.03 165.79 82.61	,
49.06	•
-27.06 75.38	
75.38	
208.69 33.08 32.63	
32.63	
-19.59	
44.07	
-19.59 44.07 103.23 54.02	
23.86	-
20.00	L

FIG. 4Z SUBSTITUTE SHEET (RULE 26)

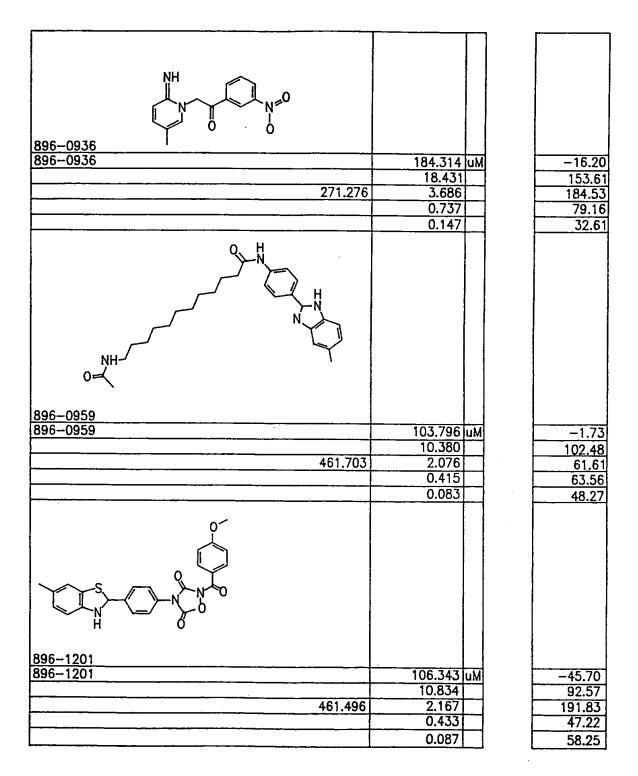


FIG. 4AA SUBSTITUTE SHEET (RULE 26)

	· •		-	
]
() s	_			
" NH		ļ		
		į		
	1			
Ţ	1			
σ ₁	1			1
I				1
	1			
896-1301		97.922		-24.32
896-1301	 +	9.792	UMI	102.49
	510 612	1.958		139.28
<u> </u>	510.612	0.392	$\vdash\vdash$	97.89
		0.332	H	23.45
		0.078	\vdash	23.43
	j		·] ·]
			ł	1
	1			
	}			1
	-		l I]
I some some]
	ļ]	ļ
/ N P]	į į
Н О .	1		 	1
			1 1	1
896-1349			<u> </u>	
896-1349		115.883	<u>luMl</u>	-39.92
		11.588		55.08
	431.47	2.318		122.68
		0.464		67.25
		0.093		3.39
				1
				1
F				
F			} }	1
NH F				1
J" \n"]
F NH			1 1	1
F. J. WM				
FTN				
•				
896-1362 896-1362		440.740	14	1 077 04
896-1362		142.749	IUM	1,073.91
	700 000	14.275 2.855	}	1,082.17
	360.266	0.57	} 	884.71 -9.82
	 			
		0.114	<u>. </u>	-20.37

FIG. 4BB SUBSTITUTE SMEET (RULE 26)

FIG. 5A **SUBSTITUTE SHEET (RULE 26)**

FIG. 5B

FIG. 6A

FIG. 6B

FIG. 6C

59-0145

MAX: 300% EC50: 0.5 μM

MAX: 270% EC50: 5 μM

MAX: 180% EC50: 5 μM

MAX: 260% EC50: 3 μM

59-0480

MAX: 180% EC50: 5 μM

FIG. 7

FIG. 8B SUBSTITUTE SHEET (RULE 20)

FIG. 8C

COMPOUND	COMPOUND CLASS	EC50	MAX RESPONSE OF 59-0008	ZGI SCORE IN Ex Vivo ASSAY	OS SCORE IN Ex Vivo ASSAY
59-0364 59-0076 59-0451 59-0472 59-0073 59-0095 59-0471 59-0030 59-0470 59-0450 59-0459 59-0064	P P P P F P Q P P P Q	0 0 0 0 ?? ?? ?? 50 uM 5 uM 5 uM	0 0 0 0 0.5x (30 uM) 0.5x (100 uM) .7x (1uM) 1.2x (100 uM) 2.7x (30 uM) 2x (10 uM) 1.5x (? uM)	1 1 1 1 1 1	1+ 1 1,1+

59-0008	Q	1 uM			1
59-0145	P	300nm	4x9	1+,2-	1+,2-
59-0106	T	300 nM	2x (9 uM)		1
59-0070	T	200 nM	2x (3 uM)		1,1+
59-0097	H	100 nM?	2x (30 uM)		1+
59-0096	H	100 nM?	4x (100 uM)		'1
59-0116	H	30 nM	2.5x (3 uM)		1+,2-
59-0210	T	30 nM	2x (3 uM)		1 1
59-0098	Н	20 nM	2x (9uM)	1+,2+	1+,2+
59-0019	Q	10 nM	2.5x (300 nM)	1+,2-	1,1+
59-0078	Q	9 nM	4x (1 uM)		1,1
59-0045	, н	5 nM	4x (1 uM)	. 1	1 1
50-0197	Q	3 nM	2.5x (300 nM)	i	1+,2-
59-0099	T	2 nM?	3x (1 uM)	! '	1,1+
59-0282	Q	1 nM	2x (3 uM)		1+,2-
59-0203	+	+	2x (3uM)	1+,2	2,3
59-0072	Ť	300 pM	2x (uM)	1-1+	1,1+
59-0150	Q	<1 nM	5x (3 uM)	1-2?	1,17
59-0104	l T	<1 nM	2x (uM)	1+,2-	1
59-0103	 	<1 nM	2x (30 nM)	-	1,1+
59-0124	T	<1 nM	2.5x (1 uM)		1+,2-
59-0205	T	<1 nM	2x (2 uM)		1
11 1000476			'		l

H=HYDRAZONE/HYDRAZIDE (45) Q=QUINOLINE/QUINOXALINE (197) P=BIS-PYRIDINES (145)

T=BENZOTHIAZOLE (104)

FIG. 9

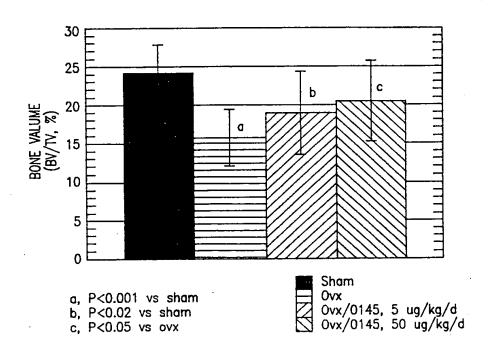


FIG. 10

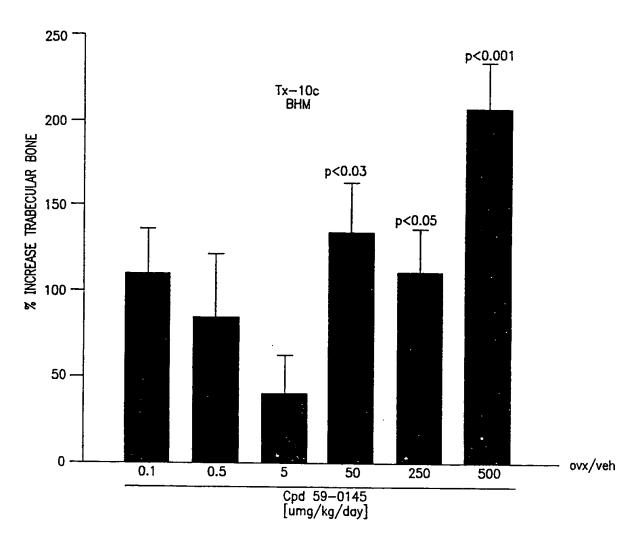


FIG. 11

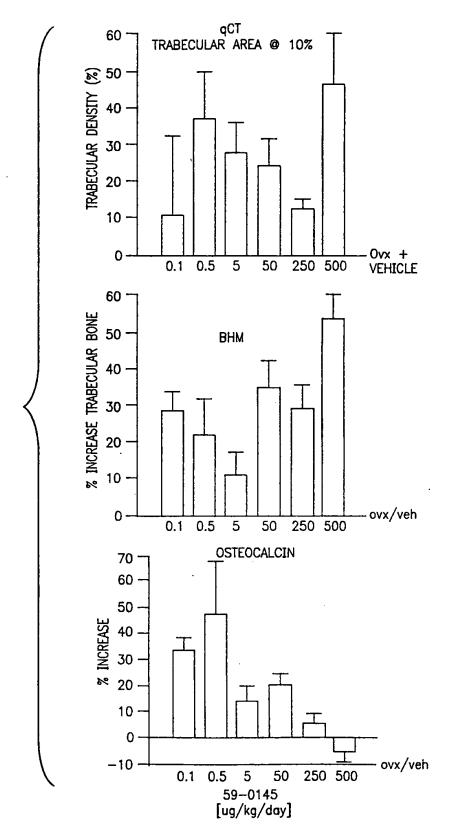


FIG. 12 Substitute sheet (rule 26)

MOLSTRUCTURE	MOL>NNC	MOL WEIGHT	NUM1
(N)	59-0020	266.732	
N			
CI	50,0004	004.707	
CI CI	59-0021	284.723	
F			
ÇH ₃	59-0022	266.367	
	į		
⇒ OH.	59-0023	239.276	
I CINC			-
i~N _N	59-0008	254.315	
S WAY			
	1		
	59-0024	220.276	
N. ~	~		
	59-0025	224.308	
CH ₃			
ľ			
CH ₃	59-0026	248.29	
	330020	240.29	
N N N N N N N N N N N N N N N N N N N			
Q	59-0027	250.303	
NH.			
	59-0028	226.283	
N'N'N			
CH ₃			
ĊHʒ			
0	59-0029	249.272	
I CINI			
		<u> </u>	

FIG. 13A SUBSTITUTE SHEET (RULE 26)

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	1 1		
	59-0031	231.3	
	59-0030	233.275	
Chilo	59-0032	248.287	
	59-0033	248.287	
OH3 NN SNN	59-0034	268.343	
СН ₃	59-0035	291.356	
Chro	59-0036	262.314	
он о	59-0037	308	
NO CH3	 		
NCH3 CH3	59-0038	241.295	
CH ₃	}		
OH SNNN	59-0039	312.352	
CH ₃	59-0040	290.368	
CH ₃ CH ₃ CH ₃ CH ₃ N CH ₃ CH ₃ N CH ₃ CH ₃ N CH ₃ N CH ₃ N	59-0041	501.902	

FIG. 13B SUBSTITUTE SHEET (RULE 26)

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	//1/4 .		
CIN-CH3	59-0042	281.36	
ON ON ON ON ON ON ON ON ON ON ON ON ON O	59-0043	280.288	
CH ₃	59-0044	341.21	
O OH CH ₃	59-0045	283.333	
CH ₃ Cl CH ₃	59-0046	389.372	
H ₃ C N-N-N	59-0047	303.367	
0 CH ₃ CH ₃ CH ₃ CH ₃	59-0048	384.501	
NO NO	59-0049	251.29	
CH ₃	59-0050	303.364	
CIN'S O	59-0051	251.353	
ON CI	59-0052	393.276	
ON CI	59-0053	354.412	
CH ₂			FIG. 13C

<u> </u>			
	59-0054	236.276	,
H ₃ C N HO O OH	59-0055	425.508	
Na+ 0 O O O O O O O O O O O O O O O O O O	59-0056	512.341	
CH ₃	59-0102	284.339	
S S N OH2	59-0057	329.448	
H ₃ C- ₀ SIN	59-0058	268.34	
S S N N S CI	59-0059	375.923	

FIG. 13D-1 SUBSTITUTE SHEET (RULE 26)

			_
OH S S CH3	59-0060	301.391	
N=N=N HO	59-0061	255.3	
N N N S	59-0062	357.44	
S N N	59-0063	255.344	
N CH ₄ CH ₁	59-0064	276.385	

FIG. 13D-2

	59-0065	254.313	
OH N S			
H ₂ N	59-0066	248.33	
N N N S	59.0067	254.315	
S S S	59-0068	259.354	
НО	59-0069	268.223	
CH ₃	59-0019	275.353	
CH ₃	59-0070	297.38	
N O CH ₃ CH ₃	59-0071	291.352	

FIG. 13E-1 SUBSTITUTE SHEET (RULE 28)

CH ₃	59-0072	330.431	
F F F F F F F F F F F F F F F F F F F	59-0073	376.303	
F CI CI F F F F F F F F F F F F F F F F	59-0074	642.735	
$F \xrightarrow{F} CI \qquad CI \qquad F \\ \downarrow N \qquad N \qquad \downarrow N \qquad \downarrow F$ $CI \qquad CI \qquad N \qquad N \qquad \downarrow N \qquad \downarrow F$	59-0075	616.775	

FIG. 13E-2

			
F CI CI F F OH F	59-0076	463.208	
F CI F F	59-0077	445.193	 . •
N CH ₃	59-0078	276.341	
	59-0079	231.297	.
0,50 N,50	59-0080	284.338	u
0 S 0 1 N CH3	59-0081	377.466	
CH ₃	59-0082	222.267	
CYNN C	59-0083	330.414	

FIG. 13F-1 SUBSTITUTE SHEET (RULE 28)

OH OH	59-0084	264.283	
OH	59-0085	278.31	
OH	59-0086	292.293	
NH2	59-0087	291.309	

FIG. 13F-2

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		<u> </u>
59-0088	263.299	
59-0089	281.357	
29-0090	324.425	
59-0091	307.394	· - .
59-0092	281.357	
	<u>-</u>	
59-0093	232.285	
59-0094	282.345	
	59-0089 29-0090 59-0091 59-0092	59-0089 281.357 29-0090 324.425 59-0091 307.394 59-0092 281.357 59-0093 232.285

FIG. 13G-1 SUBSTITUTE SHEET (RULE 20)

HO O CH3 CH3 CH3	59-0095	299.328	
HO O O CH ₃	59-0096	313.355	
HO O N-N T N CH3 CH3	59-0097	330.41	
HO CH3	59-0098	325.366	
CT _S CH ₃ CH ₃	59-0099	280.393	

FIG. 13G-2

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	59-0100	254.719	
CINCICI			
F F F	59-0101	230.232	
	<u> </u>		
CH ₃ SCH ₃	59-0103	313.379	
CH ₃	59-0104	297.312	ئ
	59-0105	267.287	
CTNNN CH3	33 0103	207.207	
0 CH3	59-0106	297.312	
	59-0107	332.378	
HO O CH ₃			
	59-0108	316.311	
HO O CH ₃			
<u> </u>	<u> </u>		

FIG. 13H-1 SUBSTITUTE SHEET (RULE 20)

HO CH ₃	59-0109	316.311	
HO O CH3	59-0110	286.286	
H ₂ N-N-CIPOH	59-0111	152.152	
CH ₃	59-0112	149.192	

FIG. 13H-2

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CH ₃	59-0113	274.365	,
H ₂ N Na O CH ₃	59-0114	475.548	
H_2^C $H_2^$	29-0115	318.87	7.
OH N CH3	59-0116	269.302	
H ₃ O CH ₃ CH ₃	59-0117	268.382	-
0 H ₂ O N	59-0118	313.354	
H ₂ O - O - CH ₃	59-0119	314.335	

FIG. 13 I - 1 SUBSTITUTE SHEET (MILE 26)

H ₃ C CH ₃	59-0120	504.485	
	59-0121	245.284	
H ₂ 0 N N N N N N N N N N N N N N N N N N N	59-0122	333.389	
H_2C H_2C H_2C O O	59-0123	347.416	
H ₂ O N O O	59-0124	350.44	

FIG. 13 I-2

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· · · · · · · · · · · · · · · · · · ·			
O-CH ₃	59-0125	372.447	
НО			
	59-0126	260.295	
СН3 Н3С-N	59-0127	329.405	
H ₃ C N CI	59-0128	436.34	
CI	59-0129	277.713	
N N N N N N N N N N N N N N N N N N N	59-0130	287.345	
N Ci Ci	59-0131	331.225	

FIG. 13J-1 SUBSTITUTE SHEET (RULE 20)

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	21/1/4			
	59-0132	313.315		
N N CH ₃	59-0133	327.342		
N-N-CI O-N-O O-CH ₃	59-0134	357.367		
0 N O O CH ₃	59-0135	356.383		
CI S N OH O	59-0136	411.868	·	

FIG. 13J-2 SUBSTITUTE SHEET (RULE 28)

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	150 0177	206 712	
CI N HO	59-0137	296.712	······································
O CH ₃	59-0138	340.808	
OL CH ₃	59-0139	340.424	
CI CI	59-0140	289.164	`
O = O = OH ₂	59-0141	437.324	
CI	59-0142	379.288	
CI P F F	590143	447.285	

FIG. 13K-1 Substitute sheet (rule 26)

N HO CH3	59-0144	316.404	
P F N N N F P	59-0145	350.265	
(INTO-C)	59-0146	246.268	
CH ₃	59-0147	314.364	
N-CH3 CH3	59-0148	291.352	

FIG. 13K-2

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	59-0149	329.335	
CH ₃	·		
CH ₃ CH ₃	59-0150	304.391	
O CH ₃	59-0151	278.31	
N N N N N N N N N N N N N N N N N N N	59-0152	266.274	
CI CI	59-0153	282.729	
CH ₃	59-0154	262.311	,
N N F F F	59-0155	316.281	

FIG. 13L-1 Substitute sheet (rule 26)

	59-0156	333.389	
CH ₃	59-0157	290.364	
H ₃ C O CH ₃	59-0158	308.335	
0-CH ₃	59-0159	308.335	
O CH ₃	59-0160	319.406	

FIG. 13L-2

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H ₂ O-N-OH ₂	59-0161	291.352	·	
	59-0162	287.321		
	59-0163	249.272		7.7
	59-0164	299.332		·
	59-0165	250.26		·
O CH ₃	59-0166	270.334		
	59-0167	263.299		

FIG. 13M-1 SUBSTITUTE SHEET (RULE 20)

	59-0168	269.346	
	59-0169	288.309	
O (N)	590170	250.26	
CINT O NEW	59-0171	238.249	
	59-0172	306.32	

FIG. 13M-2

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	59-0173	299.332	
CTNTN CH3	59-0174	279.298	
N-S N-S	59-0175	306.348	
	59-0176	256.288	
	59-0177	251.248	
	59-0178	239.237	
	59-0179	257.292	

FIG. 13N-1 SUBSTITUTE SHEET (RULE 28)

CH3	59-0180	417.487	
CH ₃	59-0181	313.358	
	59-0182	288.309	
TN TN TS	59-0183	305.36	
	59-0184	252.272	

FIG. 13N-2

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CINTHONO	59-0185	345.444			
CTS NONEF	59-0186	374.362			
OSP NCH3 CH3	59-0187	383.494			
O S CH3 CH3 CH3	59-0188	616.784			
CH ₃ CH ₃					
CH3	59-0189	490.579			-
0-CH ₃ 0-CH ₃	59-0190	550.631			-
ONCH OS OCH3 OS S=0 ONCH3 OCH3 OCH3	59-0191	584.605			
CH ₃ C CH ₃	59-0192	344.389			
CH ₃ O-CH ₃ CH ₃	59-0193	344.389			
CTS N CO-CH3	59-0194	344.389			1
- 0-снз	7		FIG.	130-	1

FIG. 130-2

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CI CI	59-0197	323.202	
CH ₃	59-0198	261.323	
O-CH ₃ O-CH ₃	59-0199	291.348	
HO O CH ₃	59-0200	342.349	
HO O CH ₃	59-0201	331.326	
S HO CH3	59-0202	300.337	
0-CH ₃	59-0203	292.336	

FIG. 13P-1 SUBSTITUTE SHEET (RULE 28)

CH ₃ CH ₃	59-0204	344.389	
CI CH3	59-0205	318.783	
CI O-CH ₃	59-0206	348.809	
0 CH ₃	59-0207	348.809	
CTSNNN FFF	59-0208	336.308	

FIG. 13P-2 SUBSTITUTE SHEET (RULE 26)

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OH OH	59-0209	247.296	
CH ₂	59-0210	297.376	
CH ₂	29-0211	264.326	
0—CH ₃ 0—CH ₃	59-0212	314.364	
CH ₃	59-0213	294.333	
CI CH3 CH3 CH3	59-0214	348.809	
CH ₃	59-0215	340.401	

FIG. 13Q-1 SUBSTITUTE SHEET (RULE 20)

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	T		
CH ₃	59-0216	264.304	
H ₂ C CH ₃ CH ₃	59-0217	278.331	
H ₂ C N CH ₃	59-0218	292.357	
H ₂ N O H ₂ O	59-0219	329.379	
HO CH ₃ O CH ₃ O CH ₃	59-0220	300.312	

FIG. 13Q-2 SUBSTITUTE SHEET (RULE 28)

HO CH ₃	59-0221	283.329	
HO CH ₃	59-0222	309.367	
HO O O OH	59-0223	284.27	•
HO CH3 O CH3 H ₂ C O CH3	59-0224	330.338	
HOOLO	59-0225	256.26	
HO O O O O O O O O O O O O O O O O O O	59-0226	285.258	
N-CH ₃	59-0227	296.396	

FIG. 13R-1 **Substitute Sheet (rule 26)**

CH ₃ CH ₃ CH ₃	59-0228	269.346	
CH ₃	59-0229	239.32	
0 N 0 CH3	59-0230	284.317	
H ₂ N	59-0231	318.399	
H ₂ C N N CH ₃	59-0232	269.35	

FIG. 13R-2

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	07174		
	59-0233	232.285	
CH ₃ CH ₃ CH ₃	59-0234	281.31	
CH ₃	59-0235	251.284	
CH ₃	59-0236	280.325	
0-CH ₃	59-0237	328.39	
CH ₃	59-0238	340.401	
HO O CH ₃	59-0239	330.338	·
HO O CH ₃	59-0240	347.393	

FIG. 13S-1 SUBSTITUTE SHEET (RULE 20)

CI N N OH OH	59-0241	344.753	,
O O S N N N	59-0242	291.286	
O-N F N O OH	59-0243	455.334	
H ₂ C CI	59-0244	414.935	

FIG. 13S-2

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H ₂ O N OH ₂	59-0245	419.887	
0H2 0 K1 0 K1 0 K1	59-0246	675.856	
CH ₃ OH N	59-0247	333.385	
HO	59-0248	247.296	
CH ₃ OCH ₃ OCH ₃	59-0249	298.297	
CI O CH3	59-0250	332.742	
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	59-0251	386.426	
HO N CH ₃	59-0252	361.376	

FIG. 13T-1 SUBSTITUTE SHEET (RULE 20)

CI CH ₃ CH ₃ CH ₃	59-0253	348.809	
H ₂ C CH ₃ CH ₃ CH ₃	59-0254	328.39	
H ₂ C ^C S N O CH ₃ CH ₃	59-0255	376.455	
HO N O CH3 O CH3 CH3	59-0256	361.376	·

FIG. 13T-2

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CI S O CH_3 CH_3 CH_3	59-0257	348.809	
H_2C O O O O O O O O O O	59-0258	344.389	
PCH3 CH3 CH3	59-0259	332.354	
H ₂ C-0 CH ₃ S N CH ₃ CH ₃	59-0260	344.389	
CH ₃	59-0261	364.423	,
F F O CH ₃ CH ₃ CH ₃	59-0262	398.36	
S O CH3	59-0263	368.455	

FIG. 13U-1 SUBSTITUTE SHEET (RULE 26)

CI S O CH3 CH3	59-0264	383.254	
Br S O CH ₃	59-0265	393.26	
H_2C S O CH_3 CH_3 CH_3	59-0266	328.39	
CH ₃	59-0267	364.423	
H ₂ C O S N O CH ₃	59-0268	358.416	

FIG. 13U-2

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$\begin{array}{c c} & & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & &$	59-0269	342.417	
CH ₃ CH ₃ CH ₃ CH ₃ CH ₃ CH ₃	59-0270	328.39	·
HO O CH ₃ O CH ₃	59-0271	360.364	
HO O CH ₃	59-0272	381.838	
0-CH ₃	59-0273	345.445	
0-CH ₃	59-0274	329.379	
$\begin{array}{c c} & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\$	59-0275	328.39	•

FIG. 13V-1 SUBSTITUTE SHEET (AULE 28)

HO TO CH3	59-0276	358.373	·
CH ₃ CH ₃ CH ₃	59-0279	327.406	
HO CH3 CH3 O CH3 O CH3	59-0277	372.375	-
HO CH ₃ O CH ₃ O CH ₃ O CH ₃ O CH ₃ O CH ₃	59-0278	372.375	
CH ₃ CH ₃ CH ₃ CH ₃	59-0280	394.352	

FIG. 13V-2

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CH ₃ CH ₃ CH ₃	59-0281	310.419	
CH ₃ CH ₃ CH ₃	59-0282	305.379	
N-N OCH3 CH3 CH3	59-0283	306.367	
CH ₃ CH ₃ CH ₃	59-0284	305.379	
N-N OCH3 CH3	59-0285	393.324	
CH ₃	59-0286	292.336	
CH ₃ OH O O	590287	306.32	

FIG. 13W-1 SUBSTITUTE SHEET (RULE 26)

CH ₃ CH ₃	59-0288	276.357	
HO O CI	59-0289	351.188	
HO JO CI	59-0290	351.188	
HO 0 CH ₃	59-0291	342.349	:
HO CH ₃ O-CH ₃ O-CH ₃	59-0292	372.375	

FIG. 13W-2

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HO O CH3	59-0293	342.349	
HO O F	59-0294	318.278	
HO O OH2	59-0295	312.323	
HO O CI	59-0296	316.743	
HO O O O O O O O O O O O O O O O O O O	59-0297	329.31	
HO O OH	59-0298	298.297	
	59-0299	304.308	

FIG. 13X-1 Substitute sheet (rule 20)

	59-0300	236.269	
	59-0301	326.35	
CI N CH3 N	59-0302	285.733	
O N CH3	59-0303	275.31	
P P N Br	59-0304	469.178	

FIG. 13X-2

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CI N N N N N N N N N N N N N N N N N N N	59-0305	340.789	
O S CH ₃	59-0306	308.403	·
/CH ₃	59-0307	300.38	
H ₂ O N S O	59-0308	304.27	
F N O CH ₃			14.
H_3C H_3C O O O O O O O O O O	59-0309	330.406	
H ₂ C H ₂ C N N F F F	59-0310	368.378	
CI N OH	59-0311	287.705	

FIG. 13Y-1 SUBSTITUTE SHEET (RULE 26)

F CI	59-0313	293.127	
F F CI	59-0314	343.134	
CI CI	59-0315	275.137	
H ₂ C N CI	59-0316	303.191	
P CI CI	59-0317	377.579	

FIG. 13Y-2

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F P	59-0318	326.679	 	
F N N N N N N N N N N N N N N N N N N N				
	59-0319	282.345		
	59-0320	206.247		
Çı	59-0321	256.691		
OH OH				-
CI	59-0322	284.745		
H ₃ C O CH ₃				
Br N Br	59-0323	285.143	 	
H ₂ C N N	59-0324	234.301		
CI N CI	59-0312	309.582		-, <u>,</u> , , , , , , , , , , , , , , , , , ,
	10 17	<u></u>	 	

FIG. 13Z-1 SUBSTITUTE SHEET (RULE 20)

	59-0325	424.505	
H_2O OH_2 OH_2 OH_2 OH_2	59-0326	404.543	
H ₂ O OH ₂ OH ₂	590327	390.517	
H_2O OH_2O	59-0328	418.57	

FIG. 13Z-2

SUBSTITUTE SHEET (RULE 20)

HO OH OH OH3	59-0329	424.53	·
H ₂ C CH ₃ OH OH O	59-0330	411.47	

FIG. I3AA

SUBSTITUTE SHEET (RULE 20)

H ₂ N-S N N	59-0354	421.419	
H ₂ C CH ₃ OH OH O	59-0342	425.497	

FIG. I3BB

SUBSTITUTE SHEET (RULE 20)

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	59-0357	351.366	
CH ₂ FF	39-0337	331.366	
F F F F F	59-0361	364.292	
F P P F	59-0362	376.255	
	59-0363	216.247	
CH ₃ CH ₃ P CH ₃ P F	59-0364	378.318	7
	59-0365	216.247	
P P S S N F P	59-0366	384.367	
FF I N N F P	59-0367	348.289	

FIG. 13CC SUBSTITUTE SHEET (RULE 26)

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· · · · · · · · · · · · · · · · · · ·			
CH ₃ CH ₃ CH ₃	59-0368	311.339	
CH ₃ CH ₃	59-0369	387.437	
CH ₃ CH ₃ CH ₃ CH ₆ CH ₆	59-0370	328.39	
HO-O CH ₃ CH ₆	59-0371	372.399	
CH ₃ CH ₃ CH ₃ CH ₃ CH ₃ CH ₃ CH ₃	59-0372	399.469	
N-N-N-NH ₂	59-0373	299.353	
CH ₃ CH ₃ CH ₃	59-0374	255.363	
CH ₃ CH ₃ CH ₃	59-0375	261.391	
H ₃ C NSO	59-0376	331.351	
	59-0377	351.408	
_H ₃ 0			

FIG. 13DD-1 Substitute sheet (rule 26)

FIG. I3DD-2

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F CI CH3	59-0380	408.813	
F CI CH3	59-0381	408.813	
F CI CH3	59-0382	408.813	
CI FF OH OBE	59-0383	468.699	
H ₃ 0 N N 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	59-0384	340.405	·
H ² O N N O CH ²	59-0385	334.377	
PF CI	59-0386	367.761	
FF CI N N N N N H ₃ C N CH	59-0387	323.729	
EE CI NO	59-0388	451.23	
<u> </u>	4 1	. ــــــــــــــــــــــــــــــــــــ	

FIG. 13EE-1 Substitute sheet (rule 28)

~	7 7	- 7	·
N	59-0389	474.268	
FF CI NO CI		., , , , ,	
CI	59-0390	487.284	
F CI NO		·	
CI	59-0391	466.245	
FF CI NO			

FIG. 13EE-2

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F Ci ON ON ON ON ON ON ON ON ON ON ON ON ON	59-0392	442.78	
F CI O O O O O O O O O O O O O O O O O O	59-0393	395.767	
F CI CI CI	59.0394	393.195	·
F CI CH3 CH3	59-0395	370.804	
F CI CI CI O	59-0396	378.18	
F CI H ₂ C ON O	59-0397	424.808	
F CI N CI	59-0398	414.234	

FIG. 13FF-1 Substitute sheet (rule 20)

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	59-0399	502.245	
F CI F F			
F CI CH3 CH3 CH3 CH3 CH3 CH3 CH3 CH3	590400	526.388	
	59-0401	364.197	
F CI CI CI			
	59-0402	362.181	
F CI CI CI			
F CI OS TCI	59-0403	538.803	

FIG. 13FF-2 SUBSTITUTE SHEET (RULE 26)

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150 0101	540 350	
59-0405	437.315	
59-0406	406.233	
59-0407	349.699	
59-0408	561.868	
59-0409	535.821	
59-0410	340.428	·
59-0411	464.294	
59-0412	429.849	
59-0413	459.874	
	59-0407 59-0408 59-0409 59-0410	59-0405 437.315 59-0406 406.233 59-0407 349.699 59-0408 561.868 59-0409 535.821 59-0410 340.428 59-0411 464.294 59-0412 429.849

FIG. 13GG-1 SUBSTITUTE SHEET (RULE 26)

F CI OS FF	59-0414	497.846	
PF CI ON ON ON ON ON ON ON ON ON ON ON ON ON	59-0415	516.905	

FIG. 13GG-2

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FF CI N CH3	59-0416	454.834	
FF CI ON CH3	59-0417	484.86	
N F O	59-0418	333.268	
N N N N CI	59-0419	367.761	
F CI HB N OH	59-0420	352.767	
F CI O	59-0421	539.339	
F F F F F F F F F F F F F F F F F F F	59-0422	351.253	
P P P P F	59-0423	385.698	·

FIG. 13HH-1 SUBSTITUTE SHEET (RULE 28)

F CI N-S CI F F	59-0424	484.186	
F CI	590425	400.186	
F CI N N N N N N N N N N N N N N N N N N	59-0426	380.756	·
F CI CI CI	59-0427	414.213	

FIG. I3HH-2

SUBSTITUTE SHEET (RULE 26)

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F CI N N	59-0428	380.756	
F CI CI N N CH3	59-0429	409.793	
F CI	59.0430	313.669	
F CI N-O CH3	59-0431	454.859 ··	
F CI CH3	59-0432	395.767	
F CI CH ₃ CH ₃ CH ₃	59-0433	407.821	

FIG. 13 II-1 SUBSTITUTE SHEET (RULE 26)

F CI N N F F F	59-0435	433.738	·
F CI N Br	59-0436	444.637	
CI F F F F F F F F F F F F F F F F F F F	59-0439	525.826	

FIG. 13 II-2

SUBSTITUTE SHEET (RULE 26)

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F CI FFF	59-0440	525.826	
CH ₂	59-0441	311.339	
NT NO NO CI	59-0442	303.704	
N-O-FF	59-0443	337.256	
	59-0444	269.259	
FF	59-0445	404.356	
F F F F	59-0446	404.356	
F F F F F F	59-0447	352.241	
	59-0448	314.39	

FIG. 13JJ-1 SUBSTITUTE SHEET (RULE 26)

\top	7	7	
F N N N N F	59-0449	394.274	
F F N N N N CH	59-0450	329.281	
F F CI F N N N N	59-0451	384.71	
F			

FIG. 13JJ-2

SUBSTITUTE SHEET (RULE 28)

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H ₃ C N N N CH ₃	59-0452	242.324		
	59-0453	214.271		
N N N N N N N N N N N N N N N N N N N	59-0454	264.291		
H ₃ C C	59-0455	300.32		
HO NH2	59-0056	308.296		
H ₂ C O N N N N CH ₂ C CH ₂	59-0457	330.342		
CH2 H2C-N N N N CH2 CH2	59-0458	300.408		
FF CH2 FF	59-0459	364.292		
FFONO	59-0460	252.238		- "
FF	59-0461	266.265		
F. CNN	59-0462	280.292		
FLNNN	59-0463	253.226	FIG.	I3KK

SUBSTITUTE SHEET (RULE 28)

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FF	59-0464	267.253	
F.F.	59-0465	363.26	
CH3 CH3 CH3	59-0466	315.352	
	59-0467	212.294	
	59-0468	213.283	
FF N N N N N F F	59-0469	378.318	
H ₂ N N N N N N N P F F	59-0470	325.293	. •
FF N-N-Q	59-0471	350.261	
FF F F F	59-0472	351.249	

FIG. 13LL SUBSTITUTE SHEET (RULE 26)

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FF N N N	59-0476	350.265		
FF (N) N N N	59-0477	283.256		
F F F	59-0478	351.253		
FLONNIN	59-0479	283.256		
FF NNNNNNN	59-0480	332.328		
F N N N F F	59-0481	363.26		
EN N N O O	59-0482	349.277		
N N KP F	59-0483	307.278		
CI CH3 CH3 CH3 CI	59-0484	315.246		
OH OH	59-0485	250.3		
PF CH3	59-0486	364.292		
Chinoff F	59-0487	302.298	FIG.	I3MM

SUBSTITUTE SHEET (RULE 26)

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PORF	59-0488	486.259	
" NON NON PE			
F‡F†	59-0489	255.3	
N SIN IN	33-0403	255.5	
CT5NN OFF	59-0490	322.309	
TNINTEF	59-0491	317.269	
CI N N N CI	590492	283.161	
F N N N N F F	59-0493	364.248	i.
Charles -	59-0494	232.285	
Ch Ckf	59-0495	299.294	
FF (N) N N N CH3	59-0496	354.33	
F N N N O CH3	59-0497	340.303	
FF	59-0498	282.268	
F N N N N CU-	59-0499	296.294	
N CH ₃			FIG. I3NN

SUBSTITUTE SHEET (RULE 28)

174A/174

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X	59-0500	316.713	

International application No. PCT/US97/18864

	SSIFICATION OF SUBJECT MATTER	<u>-</u>				
US CL.	Please See Extra Sheet. Please See Extra Sheet.					
According to	According to International Patent Classification (IPC) or to both national classification and IPC					
	DS SEARCHED					
	ocumentation searched (classification system followed	by classification symbols)				
U.S. : I	Please See Extra Sheet.					
Documentat	ion searched other than minimum documentation to the	extent that such documents are included	in the fields searched			
Electronic d	ata base consulted during the international search (na	ame of data base and, where practicable	, search terms used)			
	cture yl, bone, osteo?, BMP -diaryl, bone, osteo?, BMP					
C. DOC	UMENTS CONSIDERED TO BE RELEVANT					
Category*	Citation of document, with indication, where ap	ppropriate, of the relevant passages	Relevant to claim No.			
Y	US 5,441,964 A (BRYANT et al.) document.	15 August 1995, see entire	1-2, 5-28, 55-56			
Y	US 5,523,309 A (BRYANT et al.) document, especially claim 8.	04 June 1996, see entire	1-2, 5-28, 55-56			
Y,P	US 5,622,974 A (MUEHL) 22 April especially claim 5.	1 1997, see entire document,	1-2, 5-28, 55-56			
Y	WO 93/10113 A1 (TEIKOKU HORM May 1993, see entire document.	ONE MFG. CO., LTD.) 27	1-2, 5-28, 55-56			
Y	WO 95/10513 A1 (PFIZER INC.) document, especially claim 20.	20 April 1995, see entire	1-2, 5-30, 55-56			
Y	US 5,280,040 A (LABROO et al.) document.	18 January 1994, see entire	1-4, 31-43, 55-56			
X Furt	ner documents are listed in the continuation of Box C	See patent family annex.				
.V. 90	ecial categories of cited documents: cument defining the general state of the art which is not considered	*T* later document published after the inte date and not in conflict with the appl the principle or theory underlying the	ication but cited to understand			
to	be of particular relevance rlier document published on or after the international filing data	"X" document of particular relevance; the				
cit	*L* document which may throw doubts on priority claim(s) or which is eited to establish the publication date of another citation or other					
special reason (as specified) considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art						
P document published prior to the international filing date but later than *&* document member of the same patent family the priority date claimed						
	Date of the actual completion of the international search Date of mailing of the international search report					
28 JANUARY 1998 2 6 FEB 1998						
Commissio	Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Authorized officer					
Box PCT Washington Facsimile N	n, D.C. 20231 lo. (703) 305-3230	Telephone No. (703) 308-1235	fir			
Lacaume L	10. (193) 303-3230	, , , , , , , , , , , , , , , , , , ,	<u> </u>			

International application No.
PCT/US97/18864

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Category+	Chanon of document, with indication, where appropriate, of the relevant passages	Relevant to claim 140
ľ	Chem. abstr. Vol. 127, abstract No. 127:17703, PETRIE et al. 'Preparation of (hetero) aromatic compounds for treating bone deficit conditions', WO-97/15308 (Eng.).	1-4, 31-43, 55-56
ľ	Chem. abstr. Vol. 107, abst. No. 107:109578, WATTS et al. 'Studies on the ligand specificity and potential identity of microsomal antiestrogen-binding sites', Mol. Pharmocol. 1987, 31(5), 541-51.	1-2, 50-56
Y	Chem. abstr. Vol. 108, abstract No. 108:69162, JORDAN et al. 'Effects of antiestrogens on bone in castrated and intact female rats', Breast Cancer Res. Treat. 1987, 10(1), 31-5.	1-2, 50-56
Ý	Chem. abstr. Vol. 115, abstract No. 115:8533, SCHWARZ et al. '1,2-diphenyl-1-pyridybut-1-enes - potential antiestrogens. part 1. synthesis' Arch. Pharm. 1991, 324(4), 223-9.	1-2, 44-49, 55-56
Y	NEELAM et al. Structure-activity relationship of antiestrogens: A study using triarylbutenone, benzofuran and triayrlfuran analogues as models for triarylethylenes and triarylpropenones. J. Med. chem. 1989, Vol. 32, pages 1700-1707, see entire article.	1-2, 50-56
ď	VON ANGERER et al. Studies on heterocycle-based pure estrogen antagonists. Ann. N. Y. Academy Sciences. 1995, Vol. 761, pages 176-191, see especially pages 178-180.	1-2, 5-28, 55-56

Form PCT/ISA/210 (continuation of second sheet)(July 1992)*

International application No. PCT/US97/18864

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)
This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:
Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
2. Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).
Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)
This International Searching Authority found multiple inventions in this international application, as follows:
Please See Extra Sheet.
· ·
1. X As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
Remark on Protest
No protest accompanied the payment of additional search fces.

Form PCT/ISA/210 (continuation of first sheet(1))(July 1992)*

International application No. PCT/US97/18864

A. CLASSIFICATION OF SUBJECT MATTER:

IPC (6): A61K 31/165, 31/215, 31/33, 31/405, 31/415, 31/42, 31/425, 31/44, 31/47, 31/505, 31/53, 31/535, 31/54

A. CLASSIFICATION OF SUBJECT MATTER:

US CL: 514/222.5, 223.2, 223.8, 224.2, 226.5, 229.2, 230.5, 255, 258, 259, 296, 307, 311, 336, 345, 352, 354, 457, 365, 367, 374, 375, 385, 394, 396, 397, 415, 443, 535, 646

B. FIELDS SEARCHED

Minimum documentation searched Classification System: U.S.

514/222.5, 223.2, 223.8, 224.2, 226.5, 229.2, 230.5, 255, 258, 259, 296, 307, 311, 336, 345, 352, 354, 457, 365, 367, 374, 375, 385, 394, 396, 397, 415, 443, 535, 646

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack Unity of Invention because they are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for more than one species to be searched, the appropriate additional search fees must be paid. The claims are deemed to correspond to the species as listed in the following manner:

Group I, claims 3-4 and 31-43 compounds corresponding to Ar1 is condensed six membered heterocyclic ring, Ar2 is various aromatic rings;

Group II, claims 5-28, compounds corresponding to Ar1 is condensed five membered heterocyclic ring, Ar2 is various aromatic rings;

Group III, claims 29-30, compounds corresponding to Ar1 is isolated five membered heterocyclic ring, Ar2 is various aromatic rings;

Group IV, claims 44-49, compounds corresponding to Ar1 is isolated six membered heterocyclic ring, Ar2 is various aromatic rings;

Group V, claims 50-54, compounds corresponding to Arl is phenyl ring, Ar2 is various aromatic rings;

Group IV, claims 1-2, 55-56 in part (remaining compounds)

The following claims are generic: 1-2, 55-56

The species listed above do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2 and ANNEX B section (f), the species lack the same or corresponding special technical features for the following reasons:

The six groups of compounds corresponding to method of treating conditions of deficiency in bone growth, resorption or replacement using structurally distinctive compounds. Each group of compounds as delineated above does not share significant structural element (see Ar1, Ar2 and L are all variables, thus, not common element). In addition, at least one Markush alternative is found in CA 127:17703.

CORRECTED VERSION*

CORRECTED VERSION**



WORLD INTELLECTUAL PROPERTY ORGANIZATION International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6:	(11) Internation
A61K 31/165, 31/215, 31/33, 31/405, 31/415, 31/42, 31/425, 31/44, 31/47, 31/505, 31/53, 31/535, 31/54	(43) Internation

11) International Publication Number: WO 98/17267

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(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Applications

US 08/736,318 (CIP) Filed on 23 October 1996 (23.10.96)

(Continued on the following page)

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- (75) Inventors, Applicants (for US only): ORME, Mark, W. [US/US]; 636 N.W. 98th Street, Seattle, WA 98117 (US). BAINDUR, Nand [IN/US]; 13919 57th Place West, Edmonds, WA 98026 (US). ROBBINS, Kirk, G. [US/US]; 1200 Grant Avenue South #Y-304, Renton, WA 98055 (US). HARRIS, Scott, M. [US/US]; 6825 31st Avenue N.E., Seattle, WA 98815 (US). KONTOYIANNI, Maria [GR/US]; 769 Hayes Street #504, Seattle, WA 98109 (US). HURLEY, Laurence, H. [US/US]; 5915 Northwest Place, Austin, TX 78731 (US). KERWIN, Sean, M. [US/US]; 703 Ivy Court, Round Rock, TX 78681 (US). MUNDY, Gregory, R. [US/US]; 3719 Morgan's Creek, San Antonio, TX 78230 (US). PETRIE, Charles [US/US]; 18459 N.E. 196th Place, Woodinwille, WA 98072 (US).
- (74) Agents: MURASHIGE, Kate, H. et al.; Morrison & Foerster LLP, 2000 Pennsylvania Avenue, N.W., Washington, DC 20006-1888 (US).
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Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: COMPOSITIONS AND METHODS FOR TREATING BONE DEFICIT CONDITIONS

(57) Abstract

Compounds containing two aromatic systems covalently linked through a linker containing one or more atoms, or "linker" defined as including a covalent bond per se so as to space the aromatic systems at a distance 1.5–15Å, are effective in treating conditions associated with bone deficits. The compounds can be administered to vertebrate subjects alone or in combination with additional agents that promote bone growth or that inhibit bone resorption. They can be screened for activity prior to administration by assessing their ability to effect the transcription of a reporter gene coupled to a promoter associated with a bone morphogenetic protein and/or their ability to stimulate calvarial growth in model animal systems.

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US	08/735,881 (CIP)
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US	08/736,319 (CIP)
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Filed on	23 October 1996 (23.10.96)

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